

# **COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY**

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**HEARINGS**  
BEFORE THE  
**SUBCOMMITTEE ON MONOPOLY**  
OF THE  
**SELECT COMMITTEE ON SMALL BUSINESS**  
**UNITED STATES SENATE**  
NINETIETH CONGRESS  
SECOND SESSION  
ON  
PRESENT STATUS OF COMPETITION IN THE  
PHARMACEUTICAL INDUSTRY

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## **PART 8**

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MAY 2, 3, AND SEPTEMBER 17, 1968

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SECOND OF TWO VOLUMES ON INDOMETHACIN—  
TRADE NAME: INDOCIN



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Printed for the use of the Select Committee on Small Business

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# COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

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THURSDAY, MAY 2, 1968

U. S. SENATE,  
MONOPOLY SUBCOMMITTEE OF THE  
SELECT COMMITTEE ON SMALL BUSINESS,  
*Washington, D.C.*

The subcommittee met, pursuant to recess, at 10 a.m., in room 318, Old Senate Office Building, Senator Gaylord P. Nelson (chairman of the subcommittee) presiding.

Present: Senator Nelson.

Also present: Benjamin Gordon, staff economist; James H. Grossman, minority counsel; Susan H. Hewman, research assistant; Elaine C. Dye, research assistant; and William B. Cherkasky, legislative director, staff of Senator Nelson.

Senator NELSON. We will open our hearings.

Our witness this morning is Dr. Robert S. McCleery, Acting Director of the Division of Medical Advertising of the Bureau of Medicine of the Food and Drug Administration, and Dr. Herbert Lev.

Doctors, we appreciate your coming over here today. Dr. McCleery, you may present your testimony as you see fit. I see you have appended biographical material of your distinguished background. That will be printed in full in the record at the beginning of your statement.

(The biographical material follows:)

## BIOGRAPHICAL DATA OF ROBERT S. McCLEERY, M.D.

- 1934: A.B. (*Summa cum Laude*)—Ohio State University.  
1934: M.A. (with Highest Distinction)—Ohio State University.  
1938: M.D. (with Honors)—Ohio State University.  
1938-40: Interne and Assistant Resident—Jackson Memorial Hospital.  
1940-42: Assist. Resident in Surgery—Univ. of Minnesota Hospital.  
1942-45: U.S. Army Medical Corps.  
1945-46: Resident in Surgery—University of Minnesota Hospital.  
1946-48: Assistant Professor of Surgery—Ohio State University.  
1948-52: Associate Professor of Surgery—Vanderbilt University, and Chief of Surgery, Thayer V.A. Hospital, Nashville, Tenn.  
1952-56: Private Practice of Surgery—Great Falls, Montana.  
1956-57: Carnegie Fellow, Institute for Advanced Study and Princeton Theological Seminary.  
1957-60: Vice President and Medical Director—Burdick & Becker, Inc. (Medical Advertising), New York City.  
1960-61: Associate Medical Director—Bristol Laboratories, New York City.  
1961-62: Vice President and Medical Director—R. A. Becker, Inc. (Medical Advertising), New York City.  
1962-63: Vice President and Medical Director—Sudler & Hennessey, Inc. (Medical Advertising), New York City.  
1963- : Bureau of Medicine, Food and Drug Administration.

## MEMBERSHIPS

1. Phi Beta Kappa.
2. Alpha Omega Alpha.
3. Sigma Xi.
4. Fellow, American College of Surgeons.
5. Diplomate, American Board of Surgery.
6. Society of University Surgeons.
7. Society for Vascular Surgery.
8. Association of Medical Directors.
9. American Medical Writers Association.

## PUBLICATIONS

Research papers in the medical literature—22.

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## NOMINATION FOR DISTINGUISHED SERVICE AWARD

Name of Nominee : Robert S. McCleery, M.D.

Title of Present Position : Acting Director, Division of Medical Advertising, Office of Medical Support

Organization and Its Location : Bureau of Medicine, Food and Drug Administration, Arlington, Virginia.

Number of Years of Government Service : 12 years.

Number of Years of Service in DHEW/FDA : 5 years.

Previous Grade and Years in that Grade : GS-15 for 2 years.

Previous Grade and Years Held : GS-14 for 3 years.

Other Honors Received :

Phi Beta Kappa.

Alpha Omega Alpha.

Diplomate, American Board of Surgery.

Carnegie Fellow, Institute for Advanced Study and Princeton Theological Seminary.

FDA Award of Merit.

Citation : Dr. Robert S. McCleery is hereby awarded this Certificate for Distinguished Service. Dr. McCleery is the individual within the FDA most responsible for implementing the regulations insuring against faulty prescription drug advertising in the United States.

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## NARRATIVE STATEMENT

Education :

Ohio State University :

1930-34, A.B. (summa cum laude), Chemistry & Biology.

1934-34, M.A. (with highest distinction), Chemistry.

1934-38, M.D. (with honors).

Princeton : 1956-57, Carnegie Fellow, Institute for Advanced Study and Princeton Theological Seminary.

Honors Received :

Phi Beta Kappa : 1934.

Alpha Omega Alpha : 1938.

Diplomate, American Board of Surgery : 1947.

FDA Award of Merit : 1967.

Work Experience :

Jackson Memorial Hospital 1938-40, Miami, Florida—Intern and Assistant Resident in Surgery.

University of Minnesota Hospital, 1940-42, Minneapolis, Minnesota—Assistant Resident in Surgery.

U.S.A.M.C., 1942-45—Medical Officer.

University of Minnesota Hospital, 1945-46, Minneapolis, Minnesota—Resident in Surgery.

Ohio State University, 1946-48, Columbus, Ohio—Assistant Professor of Surgery.

Vanderbilt University, 1948-52, Nashville, Tennessee—Assistant Professor of Surgery.

Thayer VA Hospital, 1948-52, Nashville, Tennessee—Chief of Surgery.

Private practice of surgery, 1952-56, Great Falls, Montana.

Carnegie Fellow, Institute for Advanced Study and Princeton Theological Seminary, 1956-57, Princeton.

Burdick & Becker, Inc., 1957-60—Vice President and Medical Director of Medical Advertising Firm.

Bristol Laboratories, 1960-61—Associate Medical Director.

R. A. Becker, Inc., 1961-62—Vice President and Medical Director of Medical Advertising Firm.

Sudler & Hennessey, Inc., 1962-63—Vice President and Medical Director of Medical Advertising Firm.

Food and Drug Administration, Bureau of Medicine, 1963 to present, Washington, D.C., and Arlington, Va.—Medical Officer and Acting Director, Division of Medical Advertising.

**Present Position:** Administers and directs the activities of the Division of Medical Advertising, Office of Medical Support, Bureau of Medicine. Prepares or manages the preparation of advertising critiques involving complex medical features. Analyzes medical advertising and promotional labeling and makes final judgment from the Division's standpoint on the merit of cases to be forwarded for regulatory consideration. Verifies and independently searches the medical literature in relation to advertising and promotional labeling which are based on literature references. Evaluates the merit of cases in the regulatory stage and prepares comments for the assistance of General Counsel and other elements of the government as the cases proceed to completion. Develops policy and programs relating to the functions of the Division. Acts as the Agency's representative in seminars, etc. in presenting the knowledge of the Agency's responsibilities and functions for the education of the regulated industry.

**Service or Achievement Which Merits Special Honor:**

Dr. McCleery has not only competently performed all aspects of the duties required for the administration and direction of the Division of Medical Advertising, but through his most exceptional ability in dealing with complex medical issues in relation to advertising and his keen analytical ability, has contributed largely to the development of basic Agency principles on which advertising may be evaluated within the scope of the law and the regulations.

Dr. McCleery pioneered in bringing the first case under the advertising provisions of the Federal Food, Drug and Cosmetic Act to successful conclusion. In the Pree-MT case against Wallace Laboratories, which was initiated through critiques of journal advertising prepared by Dr. McCleery, the firm pleaded *nolo contendere* and was fined \$1000 on each of two counts in a criminal information.

In the Peritrate-SA case, which was initiated by Dr. McCleery, and which involved a most exacting analysis of complex advertising copy, a shipment of the drug based on misbranding through advertising was seized in 1966. Also, in 1966, the case against Serax was terminated through seizure of a shipment allegedly misbranded by advertising of the drug. Dr. McCleery's efforts in preparing the basis for seizure contributed largely in the successful completion of the case.

Dr. McCleery presented two other critiques in 1966 that resulted in seizures involving Lincolin and Lasix. Further, he sponsored action leading to the correction of many monographs in the Physicians' Desk Reference, the most important single reference book for physicians.

Dr. McCleery conceived a unique remedy for dealing with misbranding situations involving advertising or promotional labeling in the form of a "remedial letter." Early in 1967, Dr. McCleery's concept was reduced to practice. Sponsoring rapid action, Dr. McCleery presented a critique on initial advertisement for Ortho-Novum-SQ, the first advertisement for the product published after the drug was approved for marketing. Dr. McCleery's critique, charging that the ad failed to include a true statement of effectiveness of the product, resulted finally and rapidly in issuance of a "Dear Doctor" letter by the firm to other 200,000 practicing physicians in the United States.

Dr. McCleery had provided detailed guidance and counsel to the members of his staff in achieving greater effectiveness of the group in their development of critiques, searching the literature, analysis of advertising copy, etc. He has consulted in relationship to the evaluation of references, which entailed personal and independent study in many instances. For many months Dr. McCleery was the only medical officer exercising the duties of his unit. He has devoted many hours of overtime daily in keeping cur-

rent with the work of his Division. As a result of his personnel untiring efforts, the Division has not been in a backlog position on referred assignments.

The above summary of Dr. McCleery's accomplishments through 1966 was largely instrumental in his being granted the FDA Award of Merit in 1967. Beginning early in 1967, his personal participation and direction of the Division of Medical Advertising led to even greater demonstration of his effectiveness in bringing advertising and promotions of prescription drugs into compliance with the requirements of the Act.

Evidence of his success in accomplishing the mission of his Division is represented specifically in the following examples. Following the introduction of the "remedial letter" concept which corrects faulty advertising of prescription drugs, the efforts of Dr. McCleery in the areas of preparation of critiques, in participating in meetings held between the Commissioner, FDA officials and representatives of drug firms and in the development of detailed drafts of "Dear Doctor" letters, have resulted in the issuance of 20 such letters by manufacturers to all practicing physicians in the United States.

Conservatively, a total of over 4 million remedial letters have been mailed to physicians as a result of action initiated by Dr. McCleery. Copies of the 20 letters are attached to show the nature and extent of the corrections involved.

While some of the "remedial letters" involve corrections of monographs in the Physicians' Desk Reference (a comprehensive reference book used by physicians), Dr. McCleery directed the activities of his group in analyzing monographs in the book and initiating various other actions leading to correction such as issuing letter and telephone calls to firms requesting correction, participating in conferences with firms on specific problems, etc.

During the period January 1, 1967 to date over 150 corrective actions have been initiated by Dr. McCleery. In addition to "Dear Doctor" remedial letters, there have been about 93 meetings with industry representatives, 35 requests made to firms for corrective actions, one seizure (Indoklon), four prosecutions, and support given in 33 cases. Approximately 245 monographs in the Physicians' Desk Reference, and 138 prescription drug advertisements were reviewed and assessed as forerunners to remedial consideration.

In the support of cases forwarded for prosecution consideration, Dr. McCleery personally participated in citation hearings as well as in one judicial proceeding. In the latter, Dr. McCleery's testimony was considered to be largely instrumental in the success of the Government in obtaining a nolo contendere plea from the defendant and a resultant fine.

In addition to matters involving regulatory attention, Dr. McCleery provided written advice in voluntarily submitted promotional materials or other inquiries in over 80 instances.

On May 23, 1967, proposed revisions in the advertising regulations were published in the *Federal Register*. Dr. McCleery's participation in providing the basis for policy and language of those proposed regulations was a contribution of paramount importance.

Dr. McCleery's contributions to the mission of the Agency and the Department have been broadly recognized in the public press. A selection of copies of accounts in the press are attached to show the public impact of the efforts of Dr. McCleery.

The Food and Drug Administration's responsibility in the area of prescription drug advertising is a recent one. Since the passage of these regulations in 1962, Dr. McCleery has been the individual most responsible for stimulating the efforts of the Bureau of Medicine in the implementation of these regulations.

SENATOR NELSON. I assume you have no objection to being interrupted by questions from time to time?

DR. McCLEERY. No, sir.

SENATOR NELSON. Please, go ahead, Doctor.

**STATEMENT OF DR. ROBERT S. McCLEERY, ACTING DIRECTOR, DIVISION OF MEDICAL ADVERTISING, BUREAU OF MEDICINE, FOOD AND DRUG ADMINISTRATION; ACCOMPANIED BY DR. HERBERT L. LEY, DIRECTOR, BUREAU OF MEDICINE, FDA; AND WILLIAM W. GOODRICH, GENERAL COUNSEL, FDA**

Dr. McCLEERY. Mr. Chairman, I appreciate this opportunity of appearing before you this morning to discuss our experience with the advertising of Indocin.

Shortly after Dr. Goddard became Commissioner of Food and Drugs, in early 1966, the agency's interests in prescription drug advertising were sharply accentuated. It was felt that manufacturers had had time enough to adjust to new requirements concerning advertising. Dr. Goddard spoke to the presidents of pharmaceutical firms, to their medical directors and to their advertising agencies to note what we regarded as a continuation of advertising abuses that had been so largely responsible for the enactment in 1962 of the Kefauver-Harris drug amendments and the promulgation in 1964 of the first advertising regulations.

Senator NELSON. Doctor, do you have any examples that you would like to give us of what you consider to be advertising abuses, in addition to those you have already mentioned?

Dr. McCLEERY. The case we are describing today is in our view a case typical of some of the major abuses. We could submit for the record the actions we have taken against drugs in the past in terms of the use of the sanctions for criminal prosecutions—the use of seizure of products for bad advertising and for a large number of "Dear Doctor" remedial letters which have been sent, roughly 20 in number.

Senator NELSON. I would like to have the examples you referred to.

Do I understand you to say that the case you are talking about today is quite typical of other instances that you have of the same kind of advertising abuses?

Dr. McCLEERY. Well, in some sense, yes, in that it contains a number of faults which are common to many other ads against which we have acted, and these were present during the introduction and the subsequent advertising of the drug under your interest here today.

Senator NELSON. The point I am interested in having clear for the record is whether or not this is an isolated case, or whether it is a general problem that you have to deal with.

Dr. LEY. Senator Nelson, may I suggest that we submit for the record the examples of what the FDA considered misleading advertising which were presented in October of 1966 by Mr. Goodrich, and secondly, a file of "Dear Doctor" letters stimulated by the FDA over the past year. I believe this will set the picture in proper perspective.

Senator NELSON. All right. If you would submit that for the record. (The material to be furnished for inclusion in the record follows:)

**THE STATE OF THE LAW AND COMPLIANCE\***

(Address of William W. Goodrich, Assistant General Counsel, Department of Health, Education, and Welfare, Washington, D.C.)

Three years have passed since FDA first entered the world of prescription drug advertising.

We are more intrigued with what we see today, than we were by our first viewing. To borrow a quote: "We are reading more now and enjoying it less."

\*Presented at "A Morning With FDA," Pharmaceutical Advertising Club, Roosevelt Hotel, New York City, Oct. 20, 1966.

And we are more convinced than ever that there is much room for needed improvement.

Getting to know you is a refreshing experience. It has been said of you that you have a unique ability to make a virtue out of a serious side effect.

The Kefauver investigations highlighted many excesses in drug promotion. But they suggested no remedies. The Executive Branch's first reaction was to strengthen the Federal Trade Commission Act. But the Congressional response was to require stronger control under the Federal Food, Drug, and Cosmetic Act. Instead of orders to cease and desist, new sanctions of seizure, injunction and criminal penalties were provided to do this job.

While the legislative developments were fast moving—and the legislative history is relatively thin—the message was loud and clear that there had to be some basic changes in this phase of drug promotion.

President Kennedy recommended—and the Congress enacted—provisions intended to "help assure the American people . . . that the promotional material [for Rx drugs] tells the full story . . . [the] possible bad effects as well as the good—and the whole truth about therapeutic usefulness."

This is the guideline that controls our operations.

The only concession made for the special needs of advertising was that the essential information might be presented "in brief summary". This requires the presentation of information in your ads which will fairly show the effectiveness of any drug, along with any side-effects, contraindications, precautions and warnings, in a form that is brief but neither false nor misleading. The central idea is to be sure that the message that comes through to the profession strikes a proper balance in telling what the drug is for, what the limitations are upon its usefulness, and what hazards may attend its use.

Lest there be any question as to precisely what is required—the law provides that every prescription drug advertisement and any other descriptive matter issued to promote sales shall contain a true statement of—

The formula;

The established name of the drug along with the trade name;

And "such other information in brief summary relating to side effects, contraindications and effectiveness as shall be required in regulations" issued by the Secretary.

Preclearance of ads is not required except in extraordinary circumstances. The Department was authorized to specify which promotional material is labeling (requiring full disclosure) and which is advertising (requiring the brief summary).

The regulations applicable to ad content were promptly issued—but only after a confrontation with both the pharmaceutical industry and the medical profession. Both professed to believe that advertising was not educational—that it served only a reminder role—and played no part in the physician's choice of drugs when he began to write on his prescription form.

We took the more realistic view that if advertising does not sell drugs it will not continue to run.

Therefore, the major issue requiring resolution was whether the regulatory controls would extend to the entire ad—or just to the little part that the advertiser might designate as the "brief summary."

Resolution of that issue was accomplished by final regulations, supplemented by a memorandum of understanding about their intent. The whole ad was controlled.

The regulations themselves are simple indeed. They were offered as the first step in public supervision of this very vital means of communication between the drug producer and the medical profession. The controls were not set in concrete: they can and will be improved as the need appears. To that end, we are announcing new proposals that would require that all new promotions—both advertising and labeling—to be submitted as soon as they are developed for use.

In essence, our current regulations require—insofar as the selling part of the ad is concerned—four things:

A fair summary of the effectiveness of the drug in the conditions for which it is offered, along with all of the side effects, contraindications, precautions, and warnings applicable both to the conditions for which the drug is advertised and for which it is commonly prescribed:

A fair balance in presenting the information on effectiveness and the related information on side effects, etc.:

A reasonably close association of the information on effectiveness and the information on side-effects, contraindications, etc., together with a discussion of the adverse data in the same degree of prominence that is achieved for the claims of effectiveness:

And the use of only those promotional claims which have been approved in advance upon the clearance of the drug for the market as a "new drug" or as a certified antibiotic, or, for drugs that required no pre-clearance, claims of effectiveness that are generally recognized as true or which are supported by substantial evidence, consisting of adequate and well-controlled investigations or adequate clinical experience on the basis of which it can fairly and responsibly be concluded that the drug will have the effectiveness claimed. This is not a very big order.

Simply stated, drugs may be promoted only on the basis of proven effectiveness. The total advertising message must be fair and frank in discussing both the usefulness and the hazards that may attend the administration of the drug.

And the layout of the ad must deal fairly with the scientific data that underlies the message.

As Dr. Goddard said in his Chicago speech to the Midwest PA Club, we have difficulty in understanding how a group of creative people with the talents you so regularly display should have any difficulty at all in understanding the advertising restrictions of our regulations.

"Fair balance", "reasonably close association", and the "same relative degree of prominence" are words of ordinary English.

No more inflexible words were used because the Agency wanted to move with the drug industry and the creative people in correcting what was an indefensible state of drug promotion.

If these concepts in the present regulations seem perplexing—we offer the memoranda of understanding which passed between us and the industry back in October, 1963. And we offer also a statement we made public in 1964 calling attention to the most common failings in drug promotion. More recently, at the medical section meeting of the Pharmaceutical Manufacturers Association on March 30, 1966, we described in great detail the basic premises underlying our evaluation of advertising and promotional labeling.

Bearing in mind Ben Franklin's comment that "Laws too gentle are seldom obeyed; too severe, seldom executed", we are preparing to move the informal comments in the memo of understanding and in the policy announcement into the positive provisions of regulations. And we will continue to examine the performance of all advertisers under our rules, so that misunderstanding and non-compliance can be promptly corrected.

With this background as to the state of the law, let's turn to the state of compliance by examining a few cases of actual performance.

Remembering that "all things that hurt, instruct", I apologize in advance for any injured feelings that may flow from a critical examination of some examples of your most recent work.

We would like to view with you the ads for the "big eight"—all of the eight new 1965 model drugs that entered the list of the 200 most prescribed during the first years of their introduction.

They are:

Aventyl—Eli Lilly  
C-Quens—Eli Lilly  
Indocin—Merck Sharpe Dohme  
Lincocin—Upjohn  
Oracon—Mead Johnson  
Pediamycin—Ross  
Pre-Sate—Warner Chilcott  
Tegopen—Bristol Laboratories

Without implying that there has been a complete medical work-up as to the validity of all of the advertised claims for these drugs, I can say that I asked our medical staff—including some of the physicians who were primarily responsible for the clearance of the drugs for market—to comment on some current ads for these important new offerings of the pharmaceutical industry.

Here are the results.

"No doubt, this ad will sell huge amounts of Aventyl. It is pretty, impressive, and seems to pack quite an emotional wallop. However, the term 'behavioral drift' doesn't appear to be more than a Madison Avenue description. It certainly is not a bona fide psychiatric diagnosis."

"It is, from the ad, difficult to tell in the first 4 pages, whether Aventyl is primarily an anti-depressant, primarily a tranquilizer or what."

\* \* \* \* \*

"The first sentence under side effects in both the ad and the package insert states that 'No single side effect can be considered as occurring frequently' \* \* \*."

This could lure the unsuspecting physician into not looking much further. While the incidence is mentioned later of the common side effects, it's a bit too late.

\* \* \* \* \*

"All in all, the sins in this ad are those both of omission and commission. They include poor arithmetic, poor terminology, invention of psychiatric terms, and an overwhelming intent to 'snow' the practicing physician."

As the medical officer's comment shows, we share the responsibility for some of the defects in this ad, because we approved the package insert. That does not make the ad any better.

Aventyl was offered for a new psychiatric disorder, discovered right here on Madison Avenue. While this makes excellent ad copy, it does not promote the drug for the conditions for which it has been approved. Instead, it uses a new catch phrase to cover a host of "target" symptoms, so that the drug is indicated and prescribed for the ordinary frustrations of daily living to reach a much larger patient population than the scientific data will support.

C-Quens and Oracon were approved as new sequential oral contraceptives.

The central theme of the ad for Oracon is that it is safer than and superior to other oral contraceptives because it is so close to nature—that it is physiological, natural, and normal.

These claims are unsupported by scientific facts. Thus far, there is no substantial evidence that any oral contraceptive is either more effective or safer than any other that has been approved for the market.

This ad also makes a point that Oracon was "the first sequential oral contraceptive". It fails to inform the physician that it was approved only 13 days before C-Quens. The apparent purpose of the claim is to bolster the asserted, but unsupported, superiority.

The theme of the ad for C-Quens is directed to a single side effect of the oral contraceptives—weight gain.

The claim that women using sequential oral contraceptives experience less significant weight gain is ungrounded in scientific fact, and the ad is thus misleading in its major implication. Yet, it may serve its purpose of influencing the physician to shift a patient to this product on the basis of this illusory promise.

This ad, like the one for Oracon, claims "other advantages of therapy"—presumably less side effects, and this is bolstered by a claim that it contains "the smallest amount of hormone substance". The latter claim is literally false, and the claim of lower incidence of side effects has no scientific support.

The truth about the oral contraceptives is reported in an FDA publication, available from the Government Printing Office. It is that there is no adequate scientific data, at this time, proving these compounds unsafe for human use. There are nonetheless some very infrequent but serious side effects and some possible theoretic risks suggested by the experimental data. The physician must decide for his patient whether to accept the risk—small though it may be. And the Committee which advised us said: The physician "can do this wisely only when there is presented to him dispassionate scientific knowledge of the available data."

We leave with you the question whether these two ads present the physician with "dispassionate scientific knowledge".

Indocin has been marketed for slightly more than one year. Like most new drugs offered to replace established products, this one was offered as safer and more effective. As new experience with the drug has been gained, more side-effects have been noted and more warning information has been required. Only a few days ago, the sponsor mailed a new revised brochure to the profession, with new cautionary information in heavy print. Yet the current ad continues the headline "extends the margin of safety in long term management of arthritic disorders".

There is not yet enough experience to support the claim for greater long-term safety. To the contrary, the longer the drug is used the more side-effect information appears.

This ad quotes authoritative sources, without the full impact of the actual articles. And it uses one reference which is from a 2-inch abstract, apparently of a 1964 speech. This latter reference is used to support a claim for "ankylosing spondylitis", but the ad does not inform the reader that this same abstract also states "Excellent results have also been obtained in some cases of rheumatoid arthritis . . . there have been striking failures as well."

The claim for gout is not supported by the package insert or by the scientific data.

And, finally, the "Brief Summary" omits some very important warning information that is required in the package insert—and thus in the ad.

As a side-light on this drug, it was featured in the July issue of "Pageant" magazine for "bursitis", "trick knee", "tennis elbow" and "a host of other less common disorders characterized by pain and swelling in and around the joints". The only support for these claims was user testimonials which, according to the article, were made available to the writers by the sponsor of the drug.

Lincocin is a new antibiotic entry among the 1965 models.

The ad to promote the drug is highly competitive in comparing the ease of use and the absence of some side effects expected from the established antibiotics. It is "practically painless on injection", unlike older intramuscular tetracyclines; it "does not share antigenicity with penicillin"; it has "no serious renal or neurologic abnormalities" and "no ototoxicity", unlike streptomycin or kanamycin.

Yet after such elaboration on what side effects the drug does not have, the ad obscures the most important information that the physician needs in using this drug—that hematologic toxicity can occur, and that the frequency of severe diarrhea is a unique feature of Lincocin therapy.

Pediamecin was another 1965 model antibiotic. It was featured as being especially safe for infants, but no substantial evidence existed to support the claim. And the range of its usefulness was exaggerated.

Tegopen was the final entry on the 1965 list of antibiotic drugs. The headline was "This is a new every-day penicillin for common bacterial respiratory infections".

Plainly this was to encourage indiscriminate and routine use of a drug that was approved for use primarily against penicillin resistant staph infections.

The brief summary failed to communicate the real message that it is important to identify the infectious organism and to shift to regular penicillin when the organism is later found to be sensitive to penicillin G or V.

The artwork, layout, and design of the ad was to impress the reader with the frequency with which Tegopen can be used, and not to carry the real message which the approval of the drug intended.

Pre-Sate is a new drug for the treatment of an impossible condition to treat—overeating and overweight. It is, we believe, the consensus of medical opinion that there are no true anorexiants, and that dieting is the only answer to obesity.

This attractive ad is an admirable effort to crack this attractive market. While page 6 emphasizes the essential need for concurrent diet control, the total message is that Pre-Sate is a drug of superior efficacy in reducing body weight. Statistical data is offered to prove the superiority of this drug over its established competitors. Animal data are used to support the claim that the mechanism of its action has been established.

But the claims of superiority and that it acts on the human satiety center of the hypothalamus are not scientifically established.

It is generally assumed that the 1962 Amendment did not control "relative efficacy", but ads which make claims of that kind are subject to critical review and proof that the Company's claims of superior effectiveness are well founded.

This ad appeared about the time of the Peritrate seizure. We are pleased to note improvements in later presentations.

Advertising prescription drugs should be a very special operation—wholly unlike advertising the 1967 model automobiles or the tars and nicotine of cigarettes. It should be based on the scientific data that allowed the drug to enter the market—you need look and can look no further than the official brochure for the allowable claims and the required warnings. As tempted as you may be by a new piece of investigative work that may be whispered to you to mount a new campaign to capture an entire market, you must remember that the approved claims are the limits beyond which promotion cannot go.

And in promoting newly developed and approved drugs, claims of greater safety and comparatively greater effectiveness can be made only on proven data—and then only with complete awareness that the limited experience with the drug accumulated during its investigational clinical practice; that clinical experience must be followed very closely and that ad campaigns will have to change as rapidly as clinical experience may require.

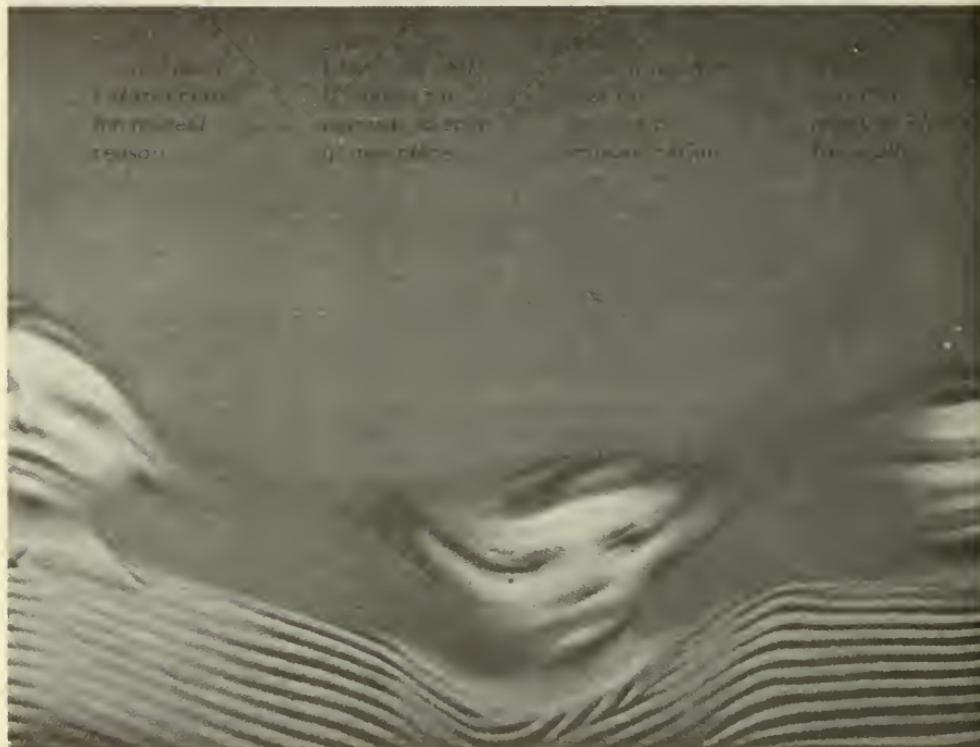
Please remember the thoughts that prescription drug advertising can go no further than the scientific support which sustains its approval for marketing; that you have an obligation in developing ad copy to tell the whole truth—good and bad; and that the entire advertising message must be designed around these basic ideas.

If the advertising copy for the "big eight" is typical of what is going on, Madison Avenue's new disease of "Behavioral Drift" is out of hand. Perhaps it can be cured by the placebo of talk, but more likely some stronger medicine will be necessary.

[From Journal of American Medical Association, Sept. 19, 1966, pp. 52-56]

## behavioral drift:

the fluctuating symptoms of the patient's emotional problem... Many emotional disorders are composed of a complex admixture of symptoms from both sides of the emotion spectrum. "Symptoms may change from time to time, waxing or waning under the complications of ever changing situations of daily life... To the clinician this means that the same patient may present a varying constellation of complaints...."<sup>1</sup>





I feel  
something  
all the  
time.

I can't tell  
where I'm  
from in through  
the house.

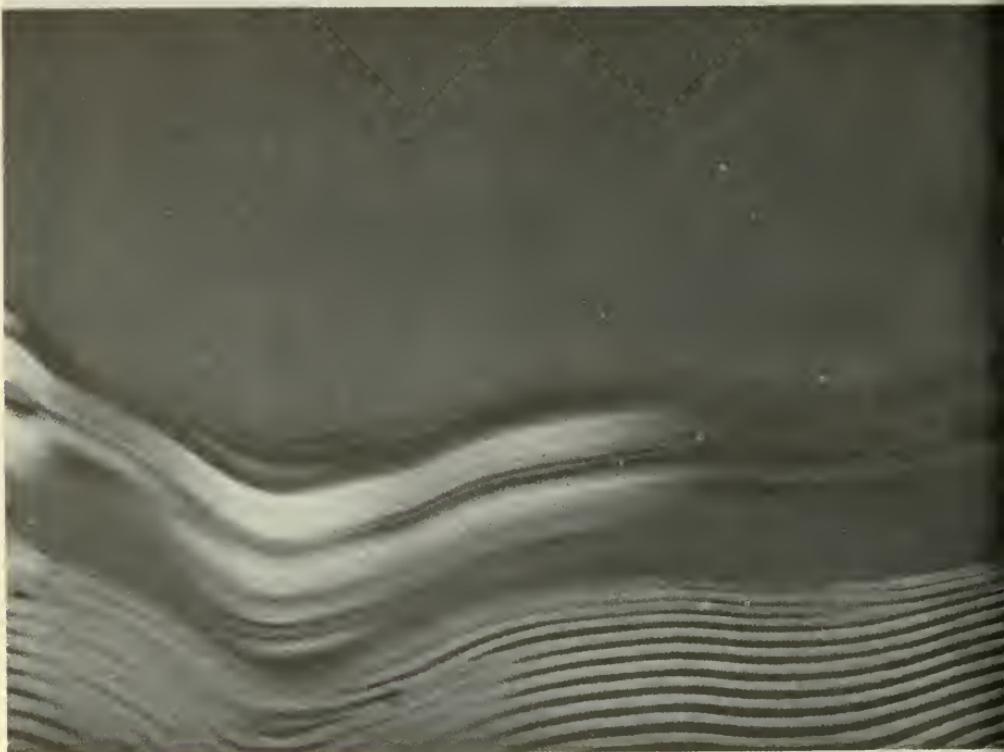
Do you  
are you  
it's not  
cancer?

when patients display  
behavioral drift:

**Aventyl HCl**  
Nortriptyline  
Hydrochloride

*Lilly*

# behavioral drift:



When the true range of usefulness of Aventyl HCl was evaluated, common presenting complaints were used as a measure of therapeutic effectiveness. As the bar graph shows, regardless of the side of the norm from which these symptoms originated, Aventyl HCl produced a high degree of satisfactory response.

when patients display  
behavioral drift:

**Aventyl® HCl**  
Nortriptyline  
Hydrochloride

*Lilly*

Three years of clinical observation confirm effectiveness of Aventyl HCl in a variety of symptoms and emotional problems<sup>2</sup>

In 1,888 patients treated with Aventyl HCl, an over-all favorable response was seen in nearly 80 percent.\*



A single-entity agent with biphasic antidepressant-antianxiety activity





## An immediate effect and a rapid over-all response

Prompt tranquilization occurs and provides evidence of initial improvement in some patients. In others, an immediate stimulatory effect is observed. Generally, a peak is rapidly reached and is soon followed by lasting over-all improvement.

Of those patients who responded to Aventyl HCl, 50 percent improved within one week, 79 percent by the second week, and 94 percent within one month.<sup>2</sup>

## Well-tolerated therapy

Unwanted effects appear to be milder and less frequent than those produced by certain other antidepressants. Studies indicate Aventyl HCl has considerably less anticholinergic activity than certain of its predecessors.

In contrast to some tranquilizers, Aventyl HCl has not been reported to cause either habituation or withdrawal symptoms.

<sup>1</sup> Cahn B. Guidelines for Understanding Emotional Disorders. *M. Times* 91:1082, 1963.

<sup>2</sup> From data available through the Lilly Research Laboratories.

when patients display behavioral drift:

# Aventyl<sup>®</sup> HCl

## Nortriptyline Hydrochloride

Additional information available  
to physicians upon request  
Eli Lilly and Company  
Indianapolis, Indiana 46207



### Actions and Indications

Aventyl HCl is a notably well-tolerated and effective agent for the treatment of mental depression, anxiety tension states, and psychoneurotic disorders and for use as an adjuvant to psychotherapy.

**Contraindications:** Concomitant use with a monoamine oxidase inhibitor is contraindicated, since potentiation of adverse effects can be serious—even fatal. The monoamine oxidase inhibitor should be discontinued for at least ten to twenty-one days before treatment with Aventyl HCl is started.

**Warnings:** Use in convulsive or hypotensive states should be closely followed. At present, data are insufficient to recommend use of Aventyl HCl during pregnancy. The possibility of a suicidal attempt in a depressed patient should always be considered. Although there have been no reports of bone marrow damage or other serious effects, careful observation of the patient and periodic laboratory studies are recommended as with all new medications.

**Precautions:** Because of its anticholinergic activity, Aventyl HCl should be used cautiously in patients with glaucoma or in those having a propensity for urinary retention. Care should be exercised when Aventyl HCl is given in conjunction with sympathomimetic drugs. Its use in hypomania along with intravenous hexobarbital methamphetamine for severe anxiety has resulted in a higher than usual frequency of side effects.

As with similar drugs, it is advisable to observe for epilepticiform seizures during the initial phase of treatment.

**Side-Effects:** No single side-effect can be considered as occurring frequently and most are mild and transitory. Dry mouth was noted in 26 percent of patients, drowsiness in 11 percent. The following were seen occasionally (in 6% to 11 percent): constipation, dizziness, tremulousness, confusional state, restlessness, weakness, and blurred vision. Side effects rarely noted (in 1 to 5 percent) were epigastric distress, sweating, peculiar taste, fatigue, weight gain, weight loss, insomnia, headache, paresthesia, nausea and vomiting, rash and itching, and delayed micturition. Miscellaneous side effects were reported in less than 0.5 percent. There have been no reports of habituation or of withdrawal symptoms. No potentiation or increased incidence of side effects was observed when Aventyl HCl was used together with tranquilizers, other antidepressants (except MAO inhibitors), oral stimulants, sedatives, hypnotic preparations, and standard drugs given for primary medical disorders.

**Dosage:** Most adults respond well to 25 mg three times daily, but the dose should be adjusted to the needs of the patient. Usual dosage range (in divided doses): Adults—20 to 100 mg daily. Children—10 to 5 mg daily (1 to 2 mg per Kg of body weight). (See package literature for complete dosage information.)

[From Medical Economics, Sept. 19, 1966, pp. 34-36]



with her sequential  
oral contraceptive

C-Quens

Lacy



## Other advantages of therapy with C-Quens

minimal spotting and breakthrough bleeding  
low incidence of nausea

a menstrual cycle approaching the normal  
the smallest amount of hormonal substance



**Description:**

**Action:**

**Indication:**

**Effectiveness:**

**Contraindications:**

**Side-Effects:**

**Warning:**

**Precautions:**

**Administration and Dosage:**

**How Supplied:**

# C-Quens



Adults: 1 tablet daily for 5 days, followed by 1 tablet every other day. Efficiency and Convenience. © 1968 E. R. Lilly and Company, Indianapolis, Indiana 46296

[From Journal of American Medical Association, Sept. 5, 1966, pp. 60-61]



"follow-through" antibiotic

# in lower respiratory infections<sup>1-7</sup>

including pneumonia, bronchitis, and complications of influenza or common cold

## caused by Staph-, Strep- and Pneumococci

**practically painless on injection**—therapy may be initiated parenterally and then followed through orally without switching antibiotic.

**reactions rare, even for patients sensitive to penicillin**—does not share antigenicity with the penicillin group of compounds.

**no reports of serious renal or neurologic abnormalities; no ototoxicity.**

**no tooth discoloration to date:** tests by 40 investigators involving 2,500 patients show no tooth discoloration with Lincocin.

## L Lincocin®

### (lincomycin hydrochloride monohydrate)

**Contraindications:** Patients previously found hypersensitive to drug; patients with known pre-existing monilial infections; and, until further clinical study is made, the newborn. **Precautions:** Use of antibiotics occasionally causes overgrowth of nonsusceptible organisms. If superinfections occur, take appropriate measures. An occasional patient has developed jaundice while receiving lincomycin, although this has not been definitely shown to be drug-related. Patients receiving treatment for longer than one or two weeks should have liver function tests. One case of irreversible toxicity to the hematopoietic system and only a few cases of neutropenia and/or leukopenia have been reported; however, it is recommended that blood counts be obtained early in course of therapy and periodically thereafter. Lincomycin has been used with caution in renal insufficiency and during various stages of pregnancy; reported no ill effects on mother or fetus. Due to lack of adequate clinical data, use in patients with pre-existing kidney, liver, endocrine or metabolic diseases not recommended unless special clinical circumstances so indicate. Efficacy in rheumatic fever not established. **Side Effects:** Most frequent—loose stools or diarrhea. Cases of severe diarrhea causing drug discontinuance have been reported. Side effects of small proportion: nausea, vomiting, abdominal cramps or pain, skin rash, rectal irritation, and dizziness. The usual agents for emergency treatment should be available. **Supplied:** 500 mg. capsules; pediatric capsules, 250 mg., in bottles of 24 and 100; 2 cc. disposable syringes; 2 cc. and 10 cc. vials—each cc. of sterile solution contains lincomycin hydrochloride monohydrate equiv. to lincomycin base, 300 mg.; also 9 mg. benzyl alcohol and water for injection, q.s.; Lincocin syrup equiv. to 250 mg. per 5 cc. lincomycin base in 60 cc. and pint bottles. Lincocin pediatric drops equiv. to 250 mg. per 5 cc. lincomycin base in 30 cc. bottles with dropper. For more detailed prescribing information on this product, see the package circular or consult your Upjohn representative. ©1966 by The Upjohn Company JEC-6376-1

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**Upjohn**

The Upjohn Company, Kalamazoo, Michigan

[From Journal of American Medical Association, Sept. 5, 1966, pp. 205-228]

Certainly  
all oral contraceptives  
are highly effective  
and well tolerated  
...yet **ORACON®**  
16 White-Ethinyl Estradiol, 0.1 mg. Tablets; 5 Pink-Dimethi-  
sterone, 25 mg., and Ethinyl Estradiol, 0.1 mg. Tablets.  
**is unsurpassed...**

...physiologically  
**ORACON<sup>®</sup>**  
is so close  
to nature\*

**simulates a natural menstrual pattern**

- produces a physiologically acceptable cycle
- simulates a normal endometrial response
- induces regular and  
predictable withdrawal bleeding

...in patient benefits

# ORACON®

affords few  
side effects\*

month after month, women usually  
experience few side effects

- virtually eliminates amenorrhea
- dramatically low  
early-cycle breakthrough bleeding
- low incidence of weight gain
- significantly low  
incidence of monilial vaginitis

\*For full documentation,  
please write to The Medical Department  
Mead Johnson Laboratories, Evansville, Indiana 47721, for the  
Physician's Brochure.

# ...so close to nature

# ORACON®

16 White—Ethinyl Estradiol, 0.1 mg. Tablets; 5 Pink—Dimethisterone, 25 mg., and Ethinyl Estradiol, 0.1 mg. Tablets.

## the first sequential oral contraceptive

**Indication:** To inhibit ovulation and provide an effective oral method of contraception.

**Effectiveness:** Oral contraceptives, including ORACON, are highly effective.

**Contraindications:** Because of estrogen content, ORACON is contraindicated in known or suspected malignancy of the breasts or reproductive tract, and in young women in whom epiphysial closure is not complete. Do not use immediately postpartum in the nursing mother because of possible inhibition of lactation or estrogenic responses in the infant. Use is also contraindicated in presence of liver dysfunction or disease, and in patients with a history of thrombophlebitis, pulmonary embolism, or cerebral vascular accident.

**Warnings:** Use with caution in patients with cardiac or renal dysfunction. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a marked degree. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or if there is sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

**Precautions:** Because of insufficient evidence concerning the possible effects of ORACON in patients with a history of metabolic disease or conditions which might be aggravated by possible estrogen-induced fluid retention (such as epilepsy, migraine, asthma, and cardiac or renal disease), ORACON should be used with care in such patients. Pre-existing uterine fibroids may increase in size while using this product. Any effect of prolonged use on pituitary, ovarian, adrenal, hepatic, or uterine function awaits further studies. Discontinue before liver or endocrine function tests. Because of osteoblastic action

of estrogens, carefully observe patients with metabolic bone disease or renal disease while on ORACON. Since safety in pregnancy is not proven, any patient missing 2 consecutive periods should have pregnancy ruled out before continuing the regimen. An estrogen-induced increase in cervical mucus is frequent; patients should be so advised. Continuous use for more than 18 months is not recommended at this time. Recurring breakthrough bleeding, particularly after the first few cycles, should be reported to the physician for further investigation. As a special precaution, another method of contraception should be used during the first 7 tablet days of the first cycle, or following discontinuance of ORACON for one or more months.

**Side Effects:** Few undesirable side effects occur with ORACON: Only 4.4% of patients discontinued medication because of side effects during clinical trials. As expected with estrogen therapy, nausea was the side effect reported most frequently. Nausea, when it occurs, is usually during the first cycle and is not severe. It may be alleviated with continued therapy or by administration at bedtime, with meals, or in divided doses. Other side effects reported during clinical studies included vomiting, abdominal cramps, bloating, anorexia, malaise, breakthrough bleeding, changes in amount and/or duration of menstrual flow, mucorrhea, and amenorrhea; headache, increased and decreased libido, weight gain or loss, nervousness, breast tenderness, dizziness, edema, diarrhea, drowsiness and premenstrual tension. Two cases of thrombophlebitis were reported during clinical trials; however, a cause-and-effect relationship has not been established.

**Administration:** Counting onset of menses as Day 1, the patient starts med-

ication on Day 5 of the menstrual cycle and takes one white tablet daily from Day 5 through Day 20, then one pink tablet daily from Day 21 through Day 25. The patient should follow the dosage schedule strictly. If the regimen is interrupted, for the fullest possible protection the patient should consult her physician about the use of an additional contraceptive method for the rest of the cycle (also see Precautions). Menses usually begin 2 to 4 days after the last pink tablet has been taken. The patient starts her new cycle of medication on Day 5. If flow does not occur by the 7th day after taking the last pink tablet start the next full course of therapy on that day, thus allowing 6 days without drug. In case of breakthrough bleeding: if spotting, continue medication; if menstrual flow, discontinue medication and begin a new full course on Day 5; for recurring breakthrough bleeding or amenorrhea, see Precautions.

**Availability:** Available as 16 white and 5 pink tablets. Each white tablet contains 0.1 mg. ethinyl estradiol; each pink tablet contains 25 mg. dimethisterone plus 0.1 mg. ethinyl estradiol. Complete details on ORACON are available on request from Mead Johnson Laboratories, Evansville, Indiana 47721.

52844

**Mead Johnson**  
LABORATORIES

*Research for Life*

[From Medical World News, Feb. 12, 1965, pp. 42-43]

Because the immaturity of infants and children influences their response to disease and drugs'...

Ross Laboratories offers  
**Pediamycin®**  
erythromycin  
ethyl succinate, Ross



**Pediamycin is effective in 86% of the common bacterial infections seen in infants and children.** It is active against gram-positive cocci<sup>2-5</sup>: streptococci, including enterococci, pneumococci and most strains of staphylococci. It is also active against *Hemophilus influenzae*.<sup>6-7</sup> It has 4 to 16 times more activity against susceptible organisms than the tetracyclines and chloramphenicol.<sup>8-13</sup>

Pediamycin is especially useful in common infections of the ear, nose and throat and in respiratory infections, including bronchitis, croup and pneumonia as well as in infections in other sites, caused by susceptible organisms.

**Pediamycin has an exceptional record of safety.** Erythromycin has been called "by far the least toxic of commonly used antibiotics"<sup>14</sup> with "a minimum of side effects."<sup>15</sup> It has never been known to have an adverse effect on bone

growth, to cause tooth staining or to damage the kidneys or impair the liver. Allergic reactions are extremely infrequent. Side effects such as diarrhea, nausea and vomiting, bacterial superinfections of the G.I. tract, moniliasis are rare and mild.

**With Pediamycin the production of resistant organisms is low.** Of 1017 strains of *Staphylococcus aureus* tested in vitro, 87 percent were sensitive.<sup>16</sup> In in vitro tests of hemolytic streptococci, all of 116 strains tested were sensitive.<sup>17</sup> In a clinical study,<sup>18</sup> 20 percent of 218 strains of group A beta-hemolytic streptococci were resistant to tetracycline; none was resistant to erythromycin.<sup>18</sup>

**Pediamycin is easy to administer.** Its cherry flavor is liked by children. Pediamycin is provided as scored chewable tablets, suspension and drops, all forms which encourage cooperation in pediatric patients.

Pediamycin—an oral antibiotic especially suited  
in forms specially prepared for infants and children...  
clinically effective and exceptionally safe



**Supply:** For children: Pediamycin Chewable tablets—scored, cherry flavored 200 mg erythromycin activity. For small children and infants: Pediamycin Suspension: granules for oral suspension 60 ml bottles 200 mg erythromycin activity per teaspoonful 5 ml; full and half teaspoon measure enclosed in package. Pediamycin Drops: granules for oral suspension 30 ml bottles, 100 mg erythromycin activity per dropperful 1/2 ml, calibrated dropper enclosed in package.

**Dosage:** The recommended dosage of erythromycin for infants and young children is 15 mg to 25 mg per pound of body weight per day in four to six divided doses. For larger children the adult dosage scale of 1 to 2 grams per day, depending upon the severity of the infection, is recommended. For unusually severe or critical conditions, larger doses may be considered. **Contraindications:** Pediamycin is contraindicated for patients with a known sensitivity to erythromycin.

**Precautions:** Side effects are relatively rare. Should a patient show signs of sensitivity, appropriate countermeasures (e.g., administration of epinephrine, steroids, etc.) should be employed and the drug withdrawn. **References:** 1. Done, A. K.: in *Drugs of Choice 1964-1965* Modell, W., ed. St. Louis, The C. V. Mosby Co., 1964, p. 66. 2. Cutting, W. C.: *Handbook of Pharma-*

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ROSS LABORATORIES COLUMBUS, OHIO 43216

serving physicians who attend the needs of children from birth through adolescence

[From Journal of American Medical Association, Sept. 5, 1966]

# JAMA

VOL 197, NO 10      SEPTEMBER 5, 1966

THE JOURNAL  
of the  
American Medical Association



Marum Tateishi

International College of Surgeons

A Japanese pioneer in the use of anesthesia in surgery was Seishu Hanacka, who, 40 years before Long used ether, had removed breast cancers and kidney stones from sleeping patients. He dosed them with a narcotic compound of six plant extracts, including henbane and jimsonweed, members of the nightshade family. The method is reminiscent of much earlier attempts. This painting on silk, specially commissioned and presented to the International College of Surgeons, depicts a legend that grew around the surgeon's experiment. His elderly mother suggested that, as she expected to die shortly anyway, the proposed anesthetic be tried on her. But Hanacka administered it to his wife for, as all three agreed, he could find another wife but he could never get another mother. The painting is reproduced here to help introduce a new regular JOURNAL feature, Anesthesia Problem of the Month (p 789).

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# This is a new, everyday penicillin for common bacterial respiratory infections with extra therapeutic coverage at no extra cost.\*

**Clinical success.** Tegopen (sodium cloxacillin monohydrate) assures you a high degree of clinical success against respiratory infections. A recent comprehensive analysis of office patients administered the drug proves the point: *96% of 259 bacterial respiratory infections treated were cured or improved.<sup>1</sup>*

**\*Kills common respiratory Gram-positive cocci.** In contrast to the penicillinase-limited Gram-positive spectrum of penicillins G and V, Tegopen (sodium cloxacillin monohydrate) destroys strep, pneumo and virtually all staphylococci.

**Bactericidal in action.** Tegopen (sodium cloxacillin monohydrate) is bactericidal, killing the offending organism. In contrast, erythromycin<sup>2</sup> and triacetyloleandomycin<sup>3</sup> are essentially bacteriostatic agents.

**Minimal side effects.** There is little likelihood of dose-related toxicity with Tegopen (sodium cloxacillin monohydrate).

**Low in cost.** Even with all of its extra advantages, Tegopen (sodium cloxacillin monohydrate) is priced comparably to penicillins G and V, and 33% less than either erythromycin or triacetyloleandomycin.

**BRISTOL THERAPEUTIC SUMMARY:** For complete information, consult Official Package Circular. **Indications:** Infections due to streptococci, pneumococci and staphylococci, particularly penicillin G-resistant strains of the latter. **Contraindications:** A history of severe allergic reactions to penicillins. **Precautions:** Typical penicillin-allergic reactions may occur, particularly in hypersensitive persons. Mycotic or bacterial infections may occur. Safety for use in pregnancy is not established. Assess renal, hematopoietic and hepatic function periodically during long-term therapy. **Adverse Reactions:** Nausea, epigastric discomfort, flatulence, diarrhea, eosinophilia, and allergic manifestations. Moderate SGOT elevations have been noted. **Usual Dosage:** Adults: 250 mg. q. 6 h. Children: 50 mg./Kg./day. Children weighing more than 20 Kg. should be given the adult dose. Treat beta-hemolytic streptococcal infections for at least 10 days. Administer 1 to 2 hours before meals.

**References:** 1. Data on file at Bristol Laboratories. 2. Geraci, J.E. (Panel Discussion, M. Finland, Moderator); *Antibiot. Ann.* 1958-59: 1051, 1959. 3. Thompson, W.T., Jr.; *South. M. J.* 56:844 (Aug.) 1963.



BRISTOL LABORATORIES  
Division of Bristol-Myers Co.  
Syracuse, New York

- IN TONSILLITIS • PHARYNGITIS • OTITIS MEDIA • SINUSITIS
- BRONCHITIS • PNEUMONITIS

**new TegoPen®**  
SODIUM CLOXA**CILLIN MONOHYDRATE**



10:38 A.M.

10:42 A.M.

11:00 A.M.

**T**here is a new,  
everyday penicillin for  
common bacterial  
respiratory infections.

11:20 A.M.

An improvement  
over penicillin G and V,  
and the medium-  
spectrum antibiotics.

11:47 A.M.

Just lift the page  
at the left and read why.

12:01 P.M.

1:15 P.M.



[From Journal of American Medical Association, Oct. 18, 1965, pp. 11-16]



## a new message for man

---

a new chemical entity to satisfy...not stimulate

presenting **PRE-SATE<sup>®</sup>**

one of the most sophisticated comparative animal studies ever conducted with an appetite suppressant demonstrates<sup>1,2</sup>:

**direct action on the satiety center<sup>1,2</sup>**



SATIATED CAT NOT ELECTRICALLY STIMULATED DOES NOT EAT



SATIATED CAT ELECTRICALLY STIMULATED EATS



SATIATED PRE-SATE-TREATED CAT ELECTRICALLY STIMULATED DOES NOT EAT

**far greater duration of anorexia than amphetamine<sup>1,2</sup>**



AFTER 2 HOURS STARVED AMPHETAMINE-TREATED CAT DOES NOT EAT



AFTER 2 HOURS STARVED PRE-SATE-TREATED CAT DOES NOT EAT



AFTER 8 HOURS AMPHETAMINE-TREATED CAT NOW EATS



AFTER 8 HOURS PRE-SATE-TREATED CAT STILL DOES NOT EAT (up to 48 hours)

**no CNS stimulation<sup>1,2</sup>**



EXCESSIVE MOTOR ACTIVITY IN AMPHETAMINE-TREATED CAT



STABILITY AND NO UNUSUAL MOTOR ACTIVITY IN PRE-SATE-TREATED CAT

Two appetite centers have been identified in the hypothalamus. The lateral nucleus is associated with feeding response, the ventromedial nucleus with satiety. Pre-Sate (chlorphentermine HCl) produced electrical brain-wave patterns of satiety in cats, starved for 48 hours, similar to electrical patterns in nonstarved cats.

## chlorphentermine HCl

no appetite suppressant has ever been introduced with more extensive clinical evaluation...

Since 1960, clinical data have been gathered on over two thousand obese patients in the U.S. and thousands of obese patients in France, Germany, Scandinavia, Mexico, Argentina, Great Britain and Canada. 67 pre-introductory clinical investigations in the United States include data on the "healthy" overweight, the obese diabetic, plus obese patients with vascular disease and hypertension.<sup>1</sup>

109 investigators...thousands of patients...have reported it to be unsurpassed as a true specific for obesity in over 1000 patients—regardless of age or sex—weight loss approximated 1 lb. per week in 99% of 1121 patients, there was no untoward CNS stimulation in over 600 women, the average cumulative weight loss was as much as 29% greater than with d-amphetamine or phenmetrazine in unlike the other anorectics tested, proved as effective in women as in men in 5 carefully controlled studies of hypertensive, cardiac and diabetic patients—did not produce heart rate, blood pressure, metabolic, or hematopoietic disturbances<sup>2</sup>—no evidence of habituation or addiction thus far preoccupation with medication and the dietetic problem are minimized with 1-per-day dosage doses are not forgotten.

...nor with more favorable comparative findings

**steady weight loss,  
fewer patient "dropouts" than with  
phenmetrazine and d-amphetamine**

In hundreds of patients, there was less discontinuance of program with Pre-Sate (chlorphentermine HCl) than with phenmetrazine or d-amphetamine.

**Rate of discontinuation of program<sup>1</sup>**

	Pre-Sate	phenmetrazine	d-amphetamine
Total patients	1121	203	174
Number dropouts	57	34	13

In 6 double-blind, comparative clinical studies,<sup>1,3,4</sup> employing a single daily dose of Pre-Sate (chlorphentermine HCl), patients lost weight steadily. In over 1000 patients—regardless of age or sex—weight loss approximated 1 lb. per week, even during the difficult fifth to tenth weeks of dieting.

**More effective in women**

Pre-Sate (chlorphentermine HCl) is equally potent within all age groups, and more effective in women than d-amphetamine or phenmetrazine.<sup>1</sup>

In over 600 women, the average cumulative weight loss in pounds per week was greater than with d-amphetamine or phenmetrazine.<sup>1</sup>

age	under 21	21-30	31-45	46-60	over 60
<b>medication</b>					
Pre-Sate	1.04	1.07	0.98	0.98	0.96
chlorphentermine HCl					
placebo	.43	.41	.52	.45	.86
d-Amphetamine	.58	.32	.75	.79	1.03
phenmetrazine	.43	.89	.88	1.18	.50

## 2

**significantly fewer CNS side effects  
than with d-amphetamine<sup>1,3,5,6</sup>  
and phenmetrazine<sup>1,4</sup>**

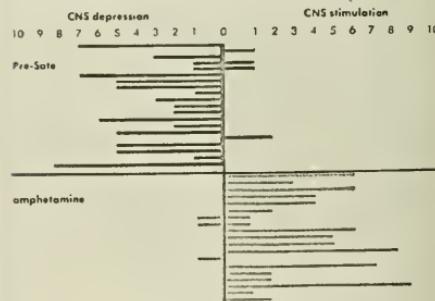
In contrast to phenmetrazine which produced a significant number of CNS side effects, Pre-Sate (chlorphentermine HCl) produced no CNS disturbances in a double-blind clinical test of 60 patients.<sup>4</sup>

Of 1,121 patients tested<sup>1</sup> with Pre-Sate (chlorphentermine HCl), 1,110 evidenced no untoward CNS stimulation.

In a double-blind, crossover study it was reported that "No evidence of central nervous system stimulation and no serious side effects developed during a four-week period on chlorphentermine [Pre-Sate]."<sup>7</sup>

In double-blind studies by 3 independent investigators Pre-Sate (chlorphentermine HCl) was found to have no untoward effect on fine coordinated movement, mental processes, or processes involving integration of special senses of sight or hearing with other centers of the central nervous system.<sup>1,8</sup> These clinical findings were corroborated in special laboratory studies employing critical "Flicker-Fusion Threshold Tests," one of the most reliable methods of measuring CNS effect of a drug.<sup>1</sup>

**Critical flicker-fusion threshold tests: Two anorectics**



This test is chiefly an index of the subject's ability to discriminate between a steady beam of light and a rapidly flickering beam of light.

In contrast to the usual stimulatory effects of the amphetamines, numerous investigators have reported the lack of such untoward effects with chlorphentermine (Pre-Sate).<sup>1,3,5,6</sup>

**new  
PRE-SATE®  
chlorphentermine HCl**

3

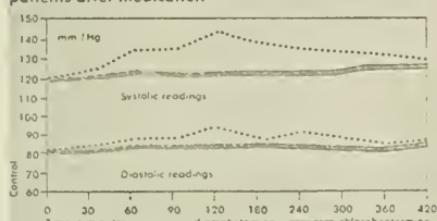
### no adverse effect on the cardiovascular parameters<sup>1,8</sup>

#### In normotensive patients

In two independent studies in overweight subjects without cardiovascular disorders, Pre-Sate (chlorphentermine hydrochloride) had no biologically significant effect on blood pressure and pulse rate.<sup>1</sup>

A third study tested the safety of a greater-than-recommended dose (100 mg.). Daily administration of the drug in this dosage for six months caused no alteration in blood pressure, pulse or ECG.<sup>1</sup>

#### Blood pressure readings of normotensive obese patients after medication



#### In patients with hypertension

Hundreds of patients with cardiovascular disorders have received Pre-Sate (chlorphentermine hydrochloride), and no adverse effects on blood pressure, ECG or pulse rate have been evidenced. Most of the patients in this category had hypertension.<sup>1</sup> These findings indicate that the drug may prove useful in treating obesity complicated by mild to moderate cardiovascular disorders; however, until continuing studies are completed, caution should be employed in its use in patients with hypertension and acute coronary disease.

#### Compared to d-amphetamine in patients with cardiovascular disorders

Russek<sup>8</sup> contrasted the frequent (85.7%) cardiovascular side effects with d-amphetamine in one group of patients to the absence of such effects in 42 obese cardiac patients who were given Pre-Sate (chlorphentermine hydrochloride), daily for periods up to 27 weeks. All patients receiving the new drug had discontinued d-amphetamine either because of side effects or contraindications.

#### Side effects in patients with cardiovascular disorders\*

	Pre-Sate	d-amphetamine
Cardiovascular disturbances	0	85.7%
CNS stimulation	2.9%	71.4%

\*Adapted from Russek, H. I.: Am. J. M. Sc. 249:305, 1965.

4

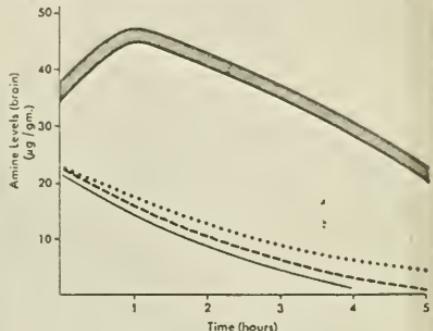
### more prolonged anorexia than with phentermine, mephentermine, d-amphetamine<sup>1,9,10</sup>

Because of the introduction of a chlorine atom in the para position, Pre-Sate (chlorphentermine HCl) is qualitatively different in pharmacologic action from all



other anorectic agents... achieves higher brain concentrations and more prolonged effect than currently available anorectics.<sup>1,9,10</sup>

#### Persistence of chlorphentermine [Pre-Sate] in brain tissue<sup>9</sup>

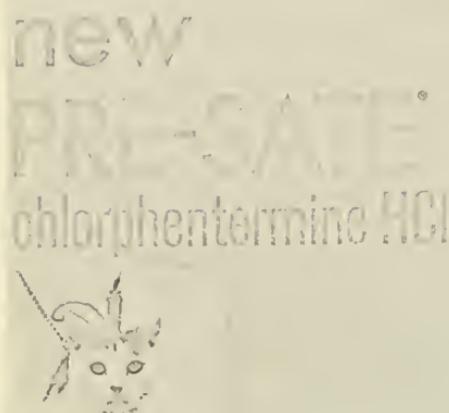


Disappearance of amines from brains of mice after a single injection (15 mg./kg., i.v.).

Each point represents the average of values obtained in 3 experiments.

— = chlorphentermine      \* \* \* = mephentermine  
--- = phentermine      — = d-amphetamine

Because Pre-Sate (chlorphentermine HCl) is an inherently long-acting molecule, appetite suppression is achieved with convenient one-per-day dosage.<sup>1</sup> Neither addiction nor habituation has occurred with Pre-Sate (chlorphentermine HCl) therapy.<sup>1</sup>



full day's anorexia  
with just one tablet  
Convenient one-per-day dosage  
—after breakfast—  
minimizes preoccupation with  
medication and the dietetic  
problem. Doses are less likely  
to be forgotten.

**Indications:** Pre-Sote (chlorphentermine HCl), a sympathomimetic amine, is indicated for the treatment of obesity, and is distinguished by a selective pattern of pharmacologic action which makes it ideal for anorectic use. This pattern of activity differs qualitatively and quantitatively from amphetamine, whose indiscriminate effects of anorectic doses on the cardiovascular system and central nervous system are well known.

**Advantages:** The anorectic action of Pre-Sote (chlorphentermine HCl), mediated through the satiety center of the hypothalamus, reduces the desire for food and makes it easier to adhere to a program of caloric reduction. Equal to other drugs in anorectic effectiveness, Pre-Sote (chlorphentermine HCl) curbs appetite without the frequency and degree of CNS stimulation caused by other anorectic drugs. Unlike the anorectic agents to which it has been compared, this new drug is as effective in women as in men.

In extensive clinical trials, this drug produced no adverse effect on blood pressure, heart rate or blood sugar. No toxic reactions have been reported and prolonged testing with greater-than-recommended dosage did not produce any evidence of alteration in renal, hepatic, hematopoietic, or cardiovascular functions during or after completion of treatment. Basal metabolic rate and blood sugar were also unaltered by the drug. Such evidence indicated that Pre-Sote (chlorphentermine HCl) may prove to be especially useful in patients who cannot tolerate the CNS stimulatory or pressor effects of other anorectic agents.

**Contraindications:** Pre-Sote (chlorphentermine HCl) is contraindicated in patients who have glaucoma, or in patients who are receiving monoamine oxidase inhibitors.

**Precautions:** As with all new drugs, physicians should be alert to the possibility of adverse reactions. The safety of Pre-Sote (chlorphentermine HCl) in human

pregnancy has not yet been established. Its use in lactating women is not recommended. Although no toxic reactions have been observed with the use of Pre-Sote (chlorphentermine HCl), physicians should be alert to the rare individual who may be overly sensitive to the drug. While clinical studies have been completed in patients with diabetes and hypertension, until continuing clinical studies are completed, caution should be employed in its use in patients with thyrotoxicosis, hypertension and acute coronary disease.

**Side effects.** Side reactions rarely complicate Pre-Sote (chlorphentermine HCl) therapy and seldom require discontinuation of medication. Throughout clinical trials, Pre-Sote (chlorphentermine HCl), in recommended dosage, has manifested a comparatively low incidence of side effects. Complaints of mydriasis, nausea, constipation, dry mouth, and, rarely, difficulty in initiating micturition, have been reported.

Paradoxically, nervousness and insomnia, and drowsiness and sedation have been reported with almost equal incidence. Headache, urticaria, and dizziness have also been reported.

**Dosage:** The recommended adult daily dose of Pre-Sote (chlorphentermine HCl) is one tablet (65 mg. chlorphentermine base as the hydrochloride), taken after the morning meal.

**How supplied:** Pre-Sote (chlorphentermine HCl) is available in bottles of 100 tablets. Each tablet contains 65 mg. chlorphentermine base as the hydrochloride.

**References:** 1. Data on file in the Medical Department of Warner-Chilcott Laboratories. 2. Emile, J. F., Shannon, J., and Warren, M. R.: *Fed. Proc.* 20: 326, 1961. 3. Fineberg, S. K.: *Am. J. Clin. Nutrition* 11: 509, 1962. 4. Rudolph, L. A., and MacLellan, I.: *Current Therap. Res.* 4: 629, 1962. 5. DiMascio, A., and Buie, D. H.: *Clin. Pharmacol. & Therap.* 5: 174, 1964. 6. Levin, J.; Trafford, J. A. P.; Newlund, P. M., and Bishop, P. M. F.: *Practitioner* 191: 65, 1963. 7. Lucy, C., and Hodden, D. R.: *Ulster M. J.* 31: 181, 1962. 8. Russek, H. I.: *Am. J. M. Sc.* 249: 305, 1965. 9. Dubnick, B.; Leron, G. A.; Leverett, R.; Morgan, D. F., and Phillips, G. E.: *J. Pharmacol. & Exper. Therap.* 140: 85, 1963. 10. Friedman, G.; Weingarten, L. A., and Jonowitz, H. D.: *Am. J. Clin. Nutrition* 10: 225, 1962.



## 21 REMEDIAL ADVERTISING LETTERS ISSUED BETWEEN JANUARY 1967 AND APRIL 1968

Firm	Drug(s)	Date of letter
Ortho.....	Ortho-Novum.....	Feb. 1, 1967.
Wallace.....	Deprol and Miltown.....	March 1967.
Roche.....	Librium.....	Do.
Abbott.....	Enduron and Enduronyl.....	April 13, 1967.
Pfizer.....	Renese, Renese-R, Rondomycin.....	May 22, 1967.
Geigy.....	Hygroton and Regroton.....	June 1967.
Mead Johnson.....	Oracon and Questran.....	June 30, 1967.
Flint.....	Choloxin.....	July 20, 1967.
Neisler.....	Diutensen-R.....	Aug. 11, 1967.
Astra.....	Cintanest.....	Aug. 23, 1967.
Squibb.....	Mysteclin-F.....	October 1967.
Organon.....	Cortropin Gel, Cortropin Zinc, Hexadrol, Hexadrol Phosphate.....	Oct. 27, 1967.
Lakeside.....	Norpramin.....	November 1967.
S. E. Massengill.....	Predsem, Salcort, Salcort-Delta.....	Nov. 1, 1967.
Upjohn.....	Medrol.....	Nov. 15, 1967.
Armour.....	H. P. Acthar Gel.....	Nov. 16, 1967.
PDR.....	H. P. Acthar Gel, Cortropin Gel, Cortropin-Zinc, Hexadrol, Hexadrol Phosphate, Norpramin, Predsem, Salcort, Salcort-Delta.	Nov. 22, 1967.
Parke-Davis.....	Pontsel.....	Jan. 5, 1968.
Syntex.....	Norguen and Norinyl.....	Jan. 22, 1968.
G. D. Searle.....	Ovulen-21.....	Jan. 26, 1968.
Geigy.....	Persantine.....	Feb. 15, 1968.

RARITAN, N.J., February 1, 1967.

DEAR DOCTOR: The Food and Drug Administration has asked us to call your attention to the fact that a claim in our recent advertising of Ortho-Novum SQ\* may be misleading.

In our introduction of this product to the medical profession we featured the theme, "The Most Effective Sequential", based on a comparison of pregnancy rates published in manufacturers' package inserts. The Food and Drug Administration has pointed out that such a comparison is invalid because there has been neither a direct comparative study of the efficacy of the three sequential oral contraceptives in the same population nor individual studies of the three products in population groups shown to be comparable. We are therefore discontinuing the promotional theme in question.

ORTHO PHARMACEUTICAL CORP.

CRANBURY, N.J.

DEAR DOCTOR: At the request of the Food and Drug Administration, we are calling your attention to one of our recent advertisements captioned, "The published clinical studies indicate: 3 of 4 non-psychotic depressions respond to 'Deprol'." The FDA considers that this advertising may have been misleading.

In the advertisement, we listed 21 studies comprising the total published 'Deprol' literature containing data on non-psychotic depressions. While the ad does not reflect the fact, data from these studies were excluded in whole or in part if—

- (a) the diagnosis was not entirely clear;
- (b) the recommended maximum dose of 6 "Deprol" tablets per day was exceeded;
- (c) other psychotropic drugs or electroshock were part of therapy.

Moderate, marked, excellent, and complete responses were counted as favorable, while mild, fair, slight, and no responses were counted as unfavorable.

Using the above criteria, the final number of patients included was 323 selected from ten of the 21 listed studies. Nine of the ten studies were uncontrolled, and most patients in the ten studies concomitantly received informal or structured psychotherapy. The reported therapeutic results (ranging from 0% in a study with two non-psychotic depressed patients, through 64% in a study with 53 patients, to 90% in two studies with 38 and 41 such patients respectively) also include, to an undetermined degree, placebo responses and spontaneous remissions known to occur in the therapy of neurotic depression.

The factors noted above represent problems that exist in working with any literature and are present in some "Miltown" advertisements carrying the theme

\*Trademark.

"one of a series". In order to avoid any misunderstanding, we have discontinued the use of these "Miltown" advertisements as well as the described "Deprol" advertisement.

Sincerely,

WALLACE PHARMACEUTICALS.

ROCHE LABORATORIES,

*Nutley, N.J.,*

DEAR DOCTOR: At the request of the Food and Drug Administration, we are extending the "brief summary" of prescribing information for Librium® (Chlordiazepoxide HC1) which appears in medical journal advertisements by adding several phrases and items from the unchanged official package circular.

The revised "brief summary" for medical journals is attached, indicating by capitalization the requested added material. Prescribing information in all Librium (chlordiazepoxide HC1) package circulars, direct mail information and brochures is complete and requires no change. The safety and effectiveness of the product are *not in question*.

In addition, in future medical journal advertisements for Librium (chlordiazepoxide HC1) in geriatric patients, we are amplifying statements which have appeared concerning possible side effects and initial dosage:

The statement that "Side effects in most instances are mild in degree and readily reversible with reduction of dosage," will be extended by the observations made in our package circular which point out that drowsiness, ataxia and confusion have been reported in some patients, particularly the elderly and debilitated, occasionally at lower dosage ranges, and that in a few instances syncope has been reported.

Whereas in geriatrics, the *usual daily dosage* is 5 mg, two to four times daily, the *initial dosage* in elderly and debilitated patients should be limited to 10 mg or less per day, adjusting as needed and tolerated.

We hope the additional detail in medical journal advertising clarifies the use of the product in accordance with the enclosed package circular.

Sincerely,

ROBERT E. DIXON, M.D.  
Director, Professional Services.

(NOTE.—This revised "brief summary" for use in future medical journal advertising contains additional phrases and items (printed in capital letters) from the official package circular which remains unchanged.)

#### BRIEF SUMMARY OF PRESCRIBING INFORMATION FOR LIBRIUM® (CHLORDIAZEPOXIDE HC1)

Before prescribing, please consult complete product information, a summary of which follows:

**Contraindications:** Patients with known hypersensitivity to the drug.

**Warnings:** Caution patients about possible combined effects with alcohol and other CNS depressants. AS WITH ALL CNS-ACTING DRUGS, CAUTION PATIENTS against hazardous occupations requiring complete mental alertness (E.G., OPERATING MACHINERY, DRIVING). THOUGH PHYSICAL AND PSYCHOLOGICAL DEPENDENCE HAVE RARELY BEEN REPORTED ON RECOMMENDED DOSES, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported. Use of any drug in pregnancy, lactation, or in women of childbearing age requires that its potential benefits be weighed against its possible hazards.

**Precautions:** In the elderly and debilitated, and in children over SIX, limit to smallest effective dosage (INITIALLY 10 MG OR LESS PER DAY) TO PRECLUDE ATAXIA OR OVERSEDATION, increasing gradually as needed and tolerated. NOT RECOMMENDED IN CHILDREN UNDER SIX. THOUGH GENERALLY NOT RECOMMENDED, IF COMBINATION THERAPY WITH OTHER PSYCHOTROPICS SEEMS INDICATED, CAREFULLY CONSIDER INDIVIDUAL PHARMACOLOGIC EFFECTS, PARTICULARLY IN USE OF POTENTIATING DRUGS SUCH AS MAO INHIBITORS AND PHENOTHIAZINES. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions, E.G., EXCITEMENT STIMULATION AND ACUTE RAGE) have been reported in psychiatric patients and hyperactive aggressive

children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies MAY BE PRESENT AND PROTECTIVE MEASURES NECESSARY. Variable effects on blood coagulations have been reported very rarely in patients receiving the drug and oral anti-coagulants; causal relationship has not been established clinically.

**Adverse Reactions:** Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. IN A FEW INSTANCES syncope HAS BEEN REPORTED. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extra-pyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reductions; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dysrasias (including agranulocytosis), jaundice and hepatic dysfunction HAVE BEEN REPORTED occasionally, making periodic blood counts and liver-function tests advisable during protracted therapy.

**Usual Daily Dosage:** Individualize for maximum beneficial effects. **Oral—** Adults: Mild and moderate anxiety and tension, 5 or 10 mg. t.i.d. or q.i.d.; severe states, 20 or 25 mg t.i.d. or q.i.d. Geriatric patients: 5 mg b.i.d. to q.i.d. (See Precautions.)

**Supplied:** Capsules, 5 mg, 10 mg and 25 mg—bottles of 50.

NORTH CHICAGO, ILL., April 13, 1967.

**DEAR DOCTOR:** The Food and Drug Administration has asked us to call your attention to a recent advertisement on Enduron® (methyclothiazide) and Enduronyl® (methyclothiazide and deserpidine). The advertisement, headlined "Thiazide-potassium problems, doctor?" is regarded by the FDA as misleading.

The ad states that the advertised drugs provide "excellent sodium output with less potassium loss than either chlorothiazide or hydrochlorothiazide."

The consensus of expert medical opinion is that there is no significant difference in the amount of potassium loss caused by thiazide agents, including methyclothiazide (Enduron).

This ad suggests that any physician taking a patient off a thiazide-potassium combination may wish to consider Enduron as alternative therapy. It states that the product will "do an outstanding job for you, without routine potassium supplementation," and that it has "potassium-sparing characteristics." The FDA believes that these claims could lead to the erroneous conclusion that hypokalemia is less likely to occur, and consequently, that potassium supplementation is less often necessary with Enduron than with other thiazides.

In point of fact, the need to consider proper potassium supplementation, dietary or otherwise, is no less with Enduron or Enduronyl than with any other thiazide drug.

Because the ad's "brief summary" of warning information was considered inadequate, a new one is enclosed.<sup>1</sup> The information capitalized in the attached revised "brief summary" is not present in current ads, but will be incorporated into future ads for these products.

ABBOTT LABORATORIES.

FLINT LABORATORIES,  
Morton Grove, Ill., July 20, 1967.

**DEAR DOCTOR:** The Food and Drug Administration has asked us to call your attention to the initial advertisements for Choloxin® (sodium dextrothyroxine), currently appearing in several journals, which are regarded by the FDA as misleading.

The headline, "A significant new advance in the management of hypercholesterolemia", does not include the qualification that Choloxin is indicated for the treatment of hypercholesterolemia in selected patients, i.e., euthyroid patients with no known evidence of organic heart disease. Also, the ad fails to stress that Choloxin is not intended to replace or to lessen the desirability of considering dietary regulation in the management of hypercholesterolemia.

The FDA points out that, while the ads emphasize that Choloxin effectively lowers blood cholesterol levels, they fail to emphasize that this effect has not been

<sup>1</sup> Retained in committee files.

proven to alter the morbidity and mortality of atherosclerotic disease. The claim in the ads that Choloxin (sodium dextrothyroxine) is "significant in its accepted physiologic mode of action" is considered to oversimplify the extent of knowledge of its mode of action. Further, the reference to "over 6,000 patients treated in clinical studies" overstates pertinent clinical experience, since only 2,967 patients were in the diagnostic categories for which the drug is currently indicated.

The FDA also considers the summary of warning information in the ads to be incomplete. The enclosed "Brief Summary" contains information in capital letters that was not present in the current ads, but will be incorporated into future ads for Choloxin. We are discontinuing the ads in question. The safety and efficacy of Choloxin are not in question when used in accordance with the official package circular, which remains unchanged.

Sincerely,

THOMAS A. GARRETT,  
Vice President, Medical Affairs.

(NOTE.—This revised "Brief Summary" for use in future medical journal advertising contains additional phrases and items (printed in capital letters) from the official package insert which remains unchanged.)

#### SUMMARY

THE USE OF CHOLOXIN® (SODIUM DEXTROTHYROXINE) DOES NOT REPLACE OR DIMINISH THE DESIRABILITY OF DIETARY MANAGEMENT OF HYPERCHOLESTEROLEMIA. THE INFLUENCE OF LOWERED SERUM CHOLESTEROL ON MORBIDITY AND MORTALITY OF ATHEROSCLEROTIC DISEASE CANNOT BE ASSESSED UNTIL LONG-TERM CLINICAL TRIALS HAVE BEEN COMPLETED.

**INDICATIONS:** THIS IS NOT AN INNOCUOUS DRUG. Strict Attention should be paid to the indications and contraindications. Indicated for treatment of hypercholesterolemia in euthyroid patients with no known evidence of organic heart disease. Also indicated for treatment of hypothyroidism in patients with cardiac disease who cannot tolerate other types of thyroid medication.

**CONTRAINDICATIONS:** (1) Known organic heart disease, INCLUDING ANGINA PECTORIS; HISTORY OF MYOCARDIAL INFARCTION; CARDIAC ARRHYTHMIA OR TACHYCARDIA, EITHER ACTIVE OR IN PATIENTS WITH DEMONSTRATED PROPENSITY FOR ARRHYTHMIAS; rheumatic heart disease; HISTORY OF CONGESTIVE HEART FAILURE; AND DECOMPENSATED OR BORDERLINE COMPENSATED CARDIAC STATUS. (2) Hypertensive states (OTHER THAN MILD, LABILE SYSTOLIC HYPERTENSION). (3) Advanced liver or kidney disease. (4) Pregnancy. (5) Nursing mothers. (6) History of iodism.

A relative contraindication is impaired liver or kidney function; WHEN EITHER OR BOTH ARE PRESENT, THE ADVANTAGES OF SODIUM DEXTROTHYROXINE THERAPY MUST BE WEIGHED AGAINST THE POSSIBILITY OF DELETERIOUS RESULTS.

**WARNINGS:** Because the effects of anticoagulants may be potentiated, REDUCE DOSAGE OF ANTICOAGULANTS BY ONE-THIRD ON INITIATION OF THERAPY and readjust as necessary ON THE BASIS OF WEEKLY TESTS OF PROTHROMBIN TIME. Concentration of Factors VII, VIII, IX, and platelet activity SHOULD ALSO BE MONITORED, since these factors may be decreased. CONSIDER WITHDRAWAL OF CHOLOXIN (SODIUM DEXTROTHYROXINE) 2 WEEKS BEFORE SURGERY IF USE OF ANTICOAGULANTS IS CONTEMPLATED.

Careful consideration of dosage schedule in hypothyroid patients WITH CARDIAC DISEASE is required, and the drug should be withdrawn or dosage reduced if AGGRAVATION OF ANGINA, INCREASED MYOCARDIAL ISCHEMIA, CARDIAC FAILURE, OR CLINICALLY SIGNIFICANT ARRHYTHMIA develops. HYPOTHYROID PATIENTS ARE MORE SENSITIVE THAN EUTHYROID PATIENTS, ESPECIALLY IF TREATED CONCOMITANTLY WITH OTHER THYROID PREPARATIONS; SPECIAL CONSIDERATION TO THE DOSAGE OF THE LATTER MUST BE GIVEN.

Thyroid preparations may enhance the effects of epinephrine injections, predisposing to arrhythmias OR CORONARY INSUFFICIENCY. DRUG WITHDRAWAL OR CAREFUL OBSERVATION OF PATIENTS RECEIVING SUCH INJECTIONS IS RECOMMENDED, ESPECIALLY BEFORE ELECTIVE SURGERY.

In diabetic patients, increased blood sugar levels may be observed, requiring upward adjustment of antidiabetic drug dosage, and SUBSEQUENT READJUSTMENT IF DEXTROTHYROXINE IS LATER WITHDRAWN.

*USE IN WOMEN OF CHILDBEARING AGE:* In women exercising birth control procedures, the drug should only be administered AFTER WEIGHING POSSIBLE RISK TO THE FETUS AGAINST POSSIBLE BENEFITS TO THE MOTHER. TERATOGENIC STUDIES IN TWO ANIMAL SPECIES HAVE BEEN NEGATIVE.

*PRECAUTIONS:* UNUSUALLY HIGH PBI VALUES ARE COMMON IN TREATED PATIENTS AND ARE NOT EVIDENCE OF HYPERMETABOLISM. IN CHILDREN, USE ONLY WHEN A SIGNIFICANT CHOLESTEROL LOWERING EFFECT IS OBSERVED. Withdrawal is indicated if iodism or new cardiac signs or symptoms develop.

*ADVERSE REACTIONS:* For the most part due to increased metabolism, AND THUS MORE COMMON IN THE HYPOTHYROID PATIENT, ESPECIALLY THE HYPOTHYROID CARDIAC. Cardiac changes have rarely been precipitated in non-cardiac patients. Angina pectoris (0.2% incidence), arrhythmia (0.5%), MYOCARDIAL ISCHEMIA (<0.1%), CARDIOMEGLY (<0.1%), FATAL AND NON-FATAL myocardial infarctions (<0.2%). Insomnia, nervousness, palpitations, tremors, WEIGHT LOSS, LID LAG, SWEATING, FLUSHING, HYPERTHERMIA, HAIR LOSS, CHANGES IN BOWEL HABITS, DIURESIS, AND MENSTRUAL IRREGULARITIES MAY ALSO BE RELATED TO THE MILD METABOLIC ACTION. A FEW PATIENTS DEVELOPED ITCHING AND SKIN RASHES, APPARENTLY FROM IODISM.

DYSPEPSIA, NAUSEA AND VOMITING, AND CHANGES IN APPETITE OCCURRED IN LESS THAN 1%. HEADACHE, CHANGES IN LIBIDO, HOARSENESS, TINNITUS, DIZZINESS, PERIPHERAL EDEMA, MALAISE, TIREDNESS, VISUAL DISTURBANCES, PSYCHIC CHANGES, PARESTHESIA, MUSCLE PAIN, AND BIZARRE COMPLAINTS WERE REPORTED IN LESS THAN 1% OF TREATED PATIENTS. GALLSTONES WERE NEWLY DISCOVERED IN 13 PATIENTS, AND CHOLESTATIC JAUNDICE IN ONE, ALTHOUGH RELATIONSHIP TO DRUG THERAPY WAS NOT ESTABLISHED. IN A TOTAL OF 19 PATIENTS, PRE-EXISTING PERIPHERAL VASCULAR DISEASE, EXOPHTHALMOS, RETINOPATHY, AND DISTURBED SENSORIUM CONTINUED TO WORSEN. CEREBROVASCULAR ACCIDENTS, THROMBOPHLEBITIS, AND G.I. HEMORRHAGES EACH OCCURRED IN LESS THAN 1% OF PATIENTS, BUT THERE APPEARS TO BE NO RELATIONSHIP TO DEXTROTHYROXINE THERAPY.

In the nearly 3,000 patients studied, the withdrawal rate was less than 3%.

*PHARMACOLOGY:* MOST EVIDENCE INDICATES THE MECHANISM OF ACTION IS TO STIMULATE THE LIVER TO INCREASE CATABOLISM OF CHOLESTEROL; SYNTHESIS OF CHOLESTEROL IS NOT INHIBITED, AND ABNORMAL METABOLIC END PRODUCTS DO NOT ACCUMULATE IN THE BLOOD.

*DOSAGE RECOMMENDATIONS:* Dosage should start at 1.0 or 2.0 mg daily to be increased monthly in 1.0 or 2.0 mg increments to a maximum of 6.0 to 8.0 mg daily if necessary for control of serum cholesterol in the adult. In hypothyroid patients, the more conservative dosage schedule should be observed. Pediatric dosage is 0.05 mg/kg daily, increased monthly in 0.05 mg/kg increments to 0.1 mg/kg or 4.0 mg daily if necessary for control.

*SUPPLIED:* 2.0 mg and 4.0 mg scored tablets in prescription bottles of 30.

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MEAD JOHNSON LABORATORIES,  
Evansville, Ind., June 30, 1967.

**DEAR DOCTOR:** The Food and Drug Administration has requested that we call your attention to current medical journal advertisements for Oracon and Questrin which the FDA regards as misleading.

#### Oracon®

The ad claims that the drug provides "... oral contraception with effects which closely parallel those of the natural hormonal cycle" and also contains a related slogan implying such effects are "So Close to Nature." The FDA points out that not nearly all effects of oral contraceptives parallel those of the natural hormonal cycle and that some of the effects of these drugs are of profound or undetermined nature.

The ad emphasizes the low incidence of certain less serious side effects such as amenorrhea, breakthrough bleeding, weight gain, etc. However, it fails to give adequate emphasis to more serious known side effects—or adequate emphasis to the possible occurrence of thrombophlebitis, pulmonary embolism or cerebral vascular accident.

The FDA points out that the pregnancy rates claimed in the ad were incorrectly based on 1065 women instead of only 880, and that the ad improperly features a pregnancy rates of 0.2 per 100 women-years. While available data do not provide a reliable scientific basis for a statement of true pregnancy rates, experience reported to us shows that the unadjusted rate for all women who were given Oracan was 2.0 per 100 women-years. The rate of 0.2 used in the ad included only those patients who insisted that they had adhered to the regimen.

#### *Questran®*

The FDA considers the summary of warning information in the journal advertisement for Questran to be inadequate in that it did not contain any information on precautions and warnings. We have attached a revised "Brief Summary," which contains the omitted precautions and warning information in capital letters.

We are discontinuing the ads in question, and future advertising will incorporate the above corrections. The safety and effectiveness of Oracan and Questran are not in question when the drugs are used in accordance with the official package inserts.

Sincerely,

P. A. WALTER, M.D.,  
*Director, Medical Research Department.*

(NOTE.—This revised "Brief Summary," for use in medical journal advertising, contains additional information, in capital letters, taken from the official package insert.)

#### BRIEF SUMMARY OF WARNING INFORMATION FOR QUESTRAN® (CHOLESTYRAMINE)

*Indication*—Questran relieves pruritus associated with partial biliary obstruction.

*Contraindication*—Patients with complete biliary obstruction.

*Warning*—ALWAYS ADMIX QUESTRAN WITH WATER OR OTHER FLUIDS BEFORE INGESTING. TO PREVENT DEFICIENCIES OF VITAMINS A, D AND K, SUPPLEMENT THE DIET, AND SEE PRECAUTIONS BELOW.

*Usage in Pregnancy*—THE SAFE USE OF QUESTRAN BY PREGNANT AND LACTATING WOMEN HAS NOT BEEN ESTABLISHED.

*Precautions*—WITH PROLONGED QUESTRAN ADMINISTRATION, GIVE VITAMINS A AND D DAILY. INCREASED BLEEDING TENDENCIES MAY DEVELOP. PROMPT RESPONSE TO PARENTERAL VITAMIN K<sub>1</sub> MAY BE ANTICIPATED. ADMINISTER CHLOROTHIAZIDE, PHENYLBUTAZONE OR WARFARIN ONE HOUR BEFORE QUESTRAN. AS A PRECAUTIONARY MEASURE, ADMINISTER ALL OTHER DRUGS 30 MINUTES TO 1 HOUR BEFORE QUESTRAN. A THEORETICAL POSSIBILITY EXISTS THAT PROLONGED USE MAY LEAD TO DEVELOPMENT OF HYPERCHOLEMIC ACIDOSIS. HERE IS NO ESTABLISHED RATIONALE FOR USE OF QUESTRAN IN THE RELIEF OF PRURITUS ASSOCIATED WITH OTHER DISEASE PROCESSES.

#### *Adverse reactions*

*Gastrointestinal and Dermatological*—Constipation, diarrhea, nausea, gastrointestinal distress, and vomiting have been reported by about 20% of patients using cholestyramine. Reported less frequently were ABDOMINAL PAIN AND DISTENTION, rash, irritation of the skin, tongue and perianal area.

*Bleeding*—In 1% of patients, increased bleeding tendencies occurred due to hypoprothrombinemia.

*Steatorrhea*—Steatorrhea occurred but rarely, and then on doses in excess of 24 grains per day.

*Cholesterol*—In patients with pruritus associated with partial biliary obstruction, serum cholesterol levels usually decrease during Questra therapy. (Clinical experience has not established the therapeutic use of Questran to reduce serum cholesterol.)

*Biliary Calcification*—Two possible instances have been observed, but a causal relationship has not been established.

ARDSLEY, N.Y.

**DEAR DOCTOR:** The Food and Drug Administration has asked us to call your attention to recent journal advertisements for our products (Hygroton® and Regroton®) which the FDA considers to be misleading.

#### *Hygroton Advertisement*

This ad is headlined, "Do your patients shell out too much for a diuretic?". It states that a published report on a new short-acting diuretic supports the claim that "If one considers maximum recommended doses for each product, tablet for tablet Hygroton was clearly superior. Two tablets of Hygroton were found to produce almost 40% more natruresis and 20% more weight loss than five tablets of the other diuretic."

The FDA points out that the studies were based on small numbers of patients (6 to 13), that the actual differences reported were clinically insignificant, and that the ad's claim for superiority was not supported by the data or by the authors' conclusions. Further, the report was not a direct comparative study of the two drugs, but rather a comparison of data obtained on the new diuretic with data obtained on Hygroton in a previous study.

In addition, the tablet-for-tablet comparison in the ad is not regarded as sound because single tablets of Hygroton and the other diuretic do not contain comparable therapeutic dosages.

#### *Regroton Advertisement*

This ad displays a single Regroton tablet in relation to two sets of five tablets representing drug regimens for treating hypertension. The ad states that "in moderate hypertension" Regroton was "better than reserpine + hydralazine + hydrochlorothiazide in 41 of 43 patients and better than reserpine + methyl-dopa + hydrochlorothiazide in 34 of 37 patients". These numbers, taken from a paper referenced in the ad, refer specifically to a comparison of average mean blood pressures after two years on Regroton with responses to prior therapy utilizing the other drug combinations.

The FDA points out that the differences observed in the blood pressure response to the various treatments were neither statistically nor clinically significant. Further, the study was not done on patients diagnosed as "moderate hypertension", and the authors did not state that the effect of Regroton on the patients' blood pressure was "better".

The FDA also considers the summary of prescribing information in each ad to be inadequate. Each enclosed "Brief Summary" contains information in capital letters that was not included in our current ads. We are discontinuing the ads in question and future advertising will incorporate the revised "Brief Summary". The safety and effectiveness of the products are not in question when used in accordance with the official package inserts.

GEIGY PHARMACEUTICALS.

(NOTE.—This revised "Brief Summary", for use in future medical journal advertising, contains additional words and phrases (printed in capital letters) taken from the official package insert.)

#### BRIEF SUMMARY OF HYGROTON®—BRAND OF CHLORTHALIDONE

**Indications:** Hypertension and many types of edema involving retention of salt and water.

**Contraindications:** Hypersensitivity and most cases of severe renal or hepatic disease.

**Warning:** With the administration of enteric-coated potassium supplements, WHICH SHOULD BE USED ONLY WHEN ADEQUATE DIETARY SUPPLEMENTATION IS NOT PRACTICAL; the possibility of small bowel lesions (OBSTRUCTION, HEMORRHAGE, AND PERFORATION) should be kept in mind. SURGERY FOR THESE LESIONS HAS FREQUENTLY BEEN REQUIRED AND DEATHS HAVE OCCURRED. DISCONTINUE ENTERIC-COATED POTASSIUM SUPPLEMENTS IMMEDIATELY IF ABDOMINAL PAIN, DISTENTION, NAUSEA, VOMITING, OR GASTROINTESTINAL BLEEDING OCCUR.

Use with caution in pregnant patients, since the drug may cross the placental barrier and adverse reactions which may occur in the adult (thrombocytopenia, hyperbilirubinemia, altered carbohydrate metabolism, etc.) are potential problems in the newborn.

**Precautions:** ANTIHYPERTENSIVE THERAPY WITH HYGROTON SHOULD ALWAYS BE INITIATED CAUTIOUSLY in postsympathectomy patients and IN PATIENTS RECEIVING GANGLIONIC BLOCKING AGENTS OR OTHER POTENT ANTIHYPERTENSIVE DRUGS, or curare. Reduce dosage of concomitant antihypertensive agents by at least one-half. Barbiturates, narcotics or alcohol may potentiate hypotension, BECAUSE OF THE POSSIBILITY OF PROGRESSION OF RENAL DAMAGE, PERIODIC DETERMINATION OF THE BUN IS INDICATED. Discontinue if the BUN rises or liver dysfunction is aggravated. HEPATIC COMA MAY PRECIPITATED.

Electrolyte imbalance, SODIUM AND/OR potassium depletion may occur. IF POTASSIUM DEPLETION SHOULD OCCUR DURING THERAPY, HYGROTON SHOULD BE DISCONTINUED AND POTASSIUM SUPPLEMENTS GIVEN, PROVIDED THE PATIENT DOES NOT HAVE MARKED OLIGURIA.

Take special care in cirrhosis or severe ischemic heart disease and in patients receiving corticosteroids, ACTH, or digitalis. Salt restriction is not recommended.

**Adverse Reactions:** Nausea, gastric irritation, vomiting, anorexia, constipation and cramping, dizziness, weakness, restlessness, hyperglycemia, hyperuricemia, headache, muscle cramps, orthostatic hypotension, aplastic anemia, leukopenia, thrombocytopenia, agranulocytosis, impotence, dysuria, transient myopia, skin rashes, urticaria, purpura, necrotizing angiitis, ACUTE GOUT, AND PANCREATITIS WHEN epigastric pain or UNEXPLAINED G.I. symptoms DEVELOP after prolonged administration. Other reactions reported with this class of compounds include: jaundice, xanthopsia, paresthesia, and photosensitization.

**Average Dosage:** One tablet (100 mg.) with breakfast daily or every other day.

**Availability:** White, single-scored tablets of 100 mg. in bottles of 100 and 1000.

(NOTE.—This revised "Brief Summary", for use in future medical journal advertising, contains additional words and phrases (printed in capital letters) taken from the official package insert.)

**BRIEF SUMMARY OF REGROTON®—CHLORTHALIDONE, 50 MG., RESERPINE U.S.P., 0.25 MG.**

**Indications:** Hypertension.

**Contraindications:** History of mental depression, hypersensitivity, and most cases of severe renal or hepatic diseases.

**Warning:** With the administration of enteric-coated potassium supplements, WHICH SHOULD BE USED ONLY WHEN ADEQUATE DIETARY SUPPLEMENTATION IS NOT PRACTICAL, the possibility of small bowel lesions (OBSTRUCTION, HEMORRHAGE, AND PERFORATION) should be kept in mind. SURGERY, FOR THESE LESIONS HAS FREQUENTLY BEEN REQUIRED AND DEATHS HAVE OCCURRED.

DISCONTINUE COATED POTASSIUM-CONTAINING FORMULATIONS IMMEDIATELY IF ABDOMINAL PAIN, DISTENTION, NAUSEA, VOMITING, OR GASTROINTESTINAL BLEEDING OCCUR.

Use cautiously during pregnancy since adverse reactions (thrombocytopenia, hyperbilirubinemia, altered carbohydrate metabolism, etc.) are potential problems in the newborn.

Discontinue 2 weeks before general anesthesia, 1 week before electroshock therapy, and if depression or peptic ulcer occurs.

**Precautions:** ANTIHYPERTENSIVE THERAPY WITH REGROTON SHOULD ALWAYS BE INITIATED CAUTIOUSLY in postsympathectomy patients and IN PATIENTS RECEIVING GANGLIONIC BLOCKING AGENTS, OTHER POTENT ANTIHYPERTENSIVE DRUGS, or curare. Reduce dosage of concomitant antihypertensive agents by at least one-half.

BECAUSE OF THE POSSIBILITY OF PROGRESSION OF RENAL DAMAGE, PERIODIC KIDNEY FUNCTION TESTS ARE INDICATED. Discontinue if the BUN rises or liver dysfunction is aggravated, HEPATIC COMA MAY BE PRECIPITATED.

Electrolyte imbalance, SODIUM AND/OR potassium depletion may occur. IF POTASSIUM DEPLETION SHOULD OCCUR DURING THERAPY, REGROTON SHOULD BE DISCONTINUED AND POTASSIUM SUPPLEMENTS GIVEN, PROVIDED THE PATIENT DOES NOT HAVE MARKED OLIGURIA.

Take particular care in cirrhosis or severe ischemic heart disease and in patients receiving corticosteroids, ACTH, or digitalis. Salt restriction is not recommended. BILIARY COLIC MAY BE PRECIPITATED (IN PATIENTS

WITH GALLSTONES) AND BRONCHIAL ASTHMA MAY OCCUR IN SUSCEPTIBLE PATIENTS.

*Adverse Reactions:* The drug is generally well tolerated. The most frequent side effects are nausea, gastrict irritation, vomiting, diarrhea, constipation, muscle cramps, headache, dizziness and ACUTE GOUT. Other potential side effects include angina pectoris, anxiety, depression, bradycardia and ectopic cardiac rhythms (especially when used with digitatilis), drowsiness, dull sensorium, hyperglycemia, hyperuricemia, lassitude, restlessness, transient myopia, impotence or dysuria, orthostatic hypotension which may be potentiated when chlorthalidone is combined with alcohol, barbiturates or narcotics, leukopenia, aplastic anemia, skin rashes, THIROMBOCYTOPENIA, AGRANULOCYTOSIS, nasal stuffiness, increased gastric secretions, nightmare, purpura, urticaria, ecchymosis, weakness, uveitis, optic atrophy and glaucoma, and PRURITUS, ERUPTIONS AND/OR FLUSHING OF THE SKIN, A REVERSIBLE PARALYSIS AGITANS-LIKE SYNDROME, INCREASED SUSCEPTIBILITY TO COLDS, DYSPNEA, weight gain, decreased libido, DRYNESS OF THE MOUTH, deafness, ANOREXIA, AND PANCREATITIS WHEN EPIGASTRIC PAIN OR UNEXPLAINED G.I. SYMPTOMS DEVELOP AFTER PROLONGED ADMINISTRATION. Jaundice, xanthopsia, PARESTHESIA, PHOTOSENSITIZATION and necrotizing angiitis ARE POSSIBLE.

*Average Dosis:* One tablet daily with breakfast.

*Availability:* Pink, single-scored tablets in bottles of 100 and 1000.

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PFIZER LABORATORIES,

New York, N.Y., May 22, 1967.

DEAR DOCTOR: The Food and Drug Administration has requested that we call your attention to recent promotional messages for our products (Rondomycin, Renese, and Renese-R) which the FDA regards as potentially misleading.

#### *Renese and Renesc-R*

The monograph in the 1967 *Physicians' Desk Reference* for Renese and Renese-R is considered inadequate in presenting information necessary for their safe and effective use. To provide you with the necessary additional information, we are enclosing a revised monograph for insertion into your *PDR*. The changes include additional warnings and precautions concerned with electrolyte imbalance, hepatic coma, maintenance dosage, and, in the case of Renese-R, the possibility of Parkinsonism and confusion.

#### *Rondomycin*

The FDA has also asked us to call to your attention certain features of our current advertising for the broad spectrum antibiotic, Rondomycin. The ad does not disclose that it is a member of the bacteriostatic tetracycline family and that administration for ten days is especially important in the treatment of Beta-hemolytic streptococcal infections. In referring to the "Protective dose (PD<sub>50</sub>) tests," the ad did not specify that they were performed in mice utilizing laboratory strains of organisms injected intraperitoneally. While demonstrating the activity of Rondomycin against these test strains, the PD<sub>50</sub> tests cannot be extrapolated directly to the clinical situation, in which sensitivity testing is recognized to be important for selection of the most appropriate antibiotic for a specific patient's infection.

In addition, the "Brief Summary" of warning information in the above ad, and also in the current journal ad for Renese-R, is considered inadequate. We are modifying the advertisements in question and future advertising will include the requested additional warning information.

Sincerely yours,

JOHN L. WATTERS, M.D.,  
Medical Director.

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NEW YORK, N.Y., August 11, 1967.

DEAR DOCTOR: The Food and Drug Administration has asked us to call your attention to a recent advertisement for Diutensen-R which the FDA regards as misleading.

The Food and Drug Administration regards the warning information in the ad to be so substantially deficient that the ad represents a potential danger to health. Therefore, we have rewritten our "Brief Summary", and the nature and extent of the changes are shown in capital letters in the attached revision. We

have discontinued the ad in question and all future ads will carry the new "Brief Summary".

The safety and efficacy of Diutensen-R are not in question when used in accordance with the prescribing information in the official package insert.

Sincerely,

NEISLER LABORATORIES.

(NOTE: This revised "Brief Summary," for use in future medical journal advertising, contains additional words and phrases (printed in capital letters) taken from the official package insert.)

#### BRIEF SUMMARY OF WARNING INFORMATION FOR DIUTENSEN-R

(For prescribing information, consult official package insert)

**Indications:** Hypertension.

**Contraindications:** SEVERE DEPRESSION and KNOWN HYPERTENSITIVITY TO reserpine, VERATRUM VIRIDE OR THIAZIDE COMPOUNDS.

**WARNING:** WITH THE ADMINISTRATION OF ENTERIC-COATED POTASSIUM SUPPLEMENTS, WHICH SHOULD BE USED ONLY WHEN ADEQUATE DIETARY SUPPLEMENTATION IS NOT PRACTICAL, THE POSSIBILITY OF SMALL BOWEL LESIONS CONSISTING OF STENOSIS WITH OR WITHOUT ULCERATION, AND CAUSING OBSTRUCTION, HEMORRHAGE, AND PERFORATION, SHOULD BE KEPT IN MIND. SURGERY FOR THESE LESIONS HAS FREQUENTLY BEEN REQUIRED AND DEATHS HAVE OCCURRED. DISCONTINUE COATED POTASSIUM-CONTAINING FORMULATIONS IMMEDIATELY IF ABDOMINAL PAIN, DISTENTION, NAUSEA, VOMITING, OR GASTROINTESTINAL BLEEDING OCCUR.

DISCONTINUE 2 WEEKS BEFORE GENERAL ANESTHESIA OR ELECTROSHOCK THERAPY, AND IF DEPRESSION OR PEPTIC ULCER OCCURS.

**Precautions:** ELECTROLYTE IMBALANCE, HYPOCHLOREMIC ALKALOSIS SODIUM AND/OR POTASSIUM DEPLETION MAY OCCUR. IF POTASSIUM DEPLETION SHOULD OCCUR DURING THERAPY, DIUTENSEN-R SHOULD BE DISCONTINUED AND POTASSIUM SUPPLEMENTS GIVEN, PROVIDED THE PATIENT DOES NOT HAVE MARKED OLIGURIA. HYPOCHLOREMIC ALKALOSIS MAY BE TREATED WITH AMMONIUM CHLORIDE IF NO LIVER DISEASE IS PRESENT.

PARTICULAR OBSERVANCE OF THE SERUM ELECTROLYTE BALANCE AND/OR POTASSIUM SUPPLEMENTATION IS NECESSARY IN PATIENTS RECEIVING HIGHER DOSAGE LEVELS, DIGITALIS, POTASSIUM DEPLETING CORTICOSTEROIDS, AND IN CIRRHOSIS ESPECIALLY WHEN THERE IS IMPENDING HEPATIC COMA.

IF PROGRESSIVE INCREASE IN SERUM NITROGEN (BUN, NPN, OR CREATININE) OCCURS, THERAPY SHOULD BE DISCONTINUED.

USE WITH CAUTION IN PATIENTS WITH A HISTORY OF PEPTIC ULCER, ULCERATIVE COLITIS, OR DEPRESSION.

DIUTENSEN-R MAY INCREASE THE POSSIBILITY OF DIGITALIS INTOXICATION. Reduce dose or discontinue if myocardial irritability occurs (extrasystoles, bigeminy or AV block).

**Adverse Reactions:** Occasional urinary frequency, nocturia, nasal congestion, DRYNESS OF THE MOUTH, muscle cramps, skin rash, joint pains due to gout, nausea, VOMITING, and dizziness.

POTENTIAL SIDE EFFECTS INCLUDE HYPERGLYCEMIA, RISE IN SERUM URIC ACID, PURPURA, THROMBOCYTOPENIA, LEUKOPENIA, PARKINSONISM, BRADCARDIA AND EXCESSIVE HYPOTENSION WITH PROSTRATION. (TREAT BRADYCARDIA WITH ATROPINE AND HYPOTENSION WITH VASOPRESSORS.) DRUG SHOULD BE DISCONTINUED IF SUFFICIENT HYPERGLYCEMIA IS OBSERVED, OR IF PURPURA, THROMBOCYTOPENIA, OR LEUKOPENIA OCCUR.

**Usual Dosage:** One tablet twice daily at morning and evening meals. Daily dosage should not exceed 4 tablets.

WORCESTER, MASS., August 23, 1967.

DEAR DOCTOR: The Food and Drug Administration has asked us to call to your attention two of our recent mailing pieces for Citanest® which the FDA regards as so substantially misleading and lacking in adequate professional use information that in its view they represent potential hazards to health

These mailing pieces, identified as 118-67 and 119-67, should be discarded if still in your possession.

### *1. Intravenous regional anesthesia*

Mailing piece 118-67 recommended the use of Citanest in intravenous regional anesthesia. The FDA regards use of this drug by that technique as experimental. The package insert for Citanest contains no information for its use in intravenous regional anesthesia and the drug has not been approved for use in that procedure.

### *2. Maximum single dosage*

Mailing pieces 118-67 and 119-67 contained statements which implied that dosages of Citanest in excess of the maximum single dose (600 mg.) could be employed in clinical use. No such implication was intended by Astra, and Astra reaffirms that no more than 600 mg. of the drug should be used during any two-hour period.

### *Professional use information*

Both booklets omitted essential and required professional use information. The attached page contains the warning, precautionary, and adverse reaction information which was omitted from the "full disclosure" sections of the booklets.

The safety and effectiveness of Citanest (prilocaine), when used in accordance with the conditions specified in the enclosed package insert, are not in question.

Sincerely yours,

ASTRA PHARMACEUTICAL PRODUCTS, INC.

ASTRA®

The following warning, precautionary, and adverse reaction information contained in the approved (November 18, 1965) Citanest labeling (identified "120" and "Issued October, 1965") is omitted from the product information text of Citanest® mailing pieces 118-67 and 119-67:

**Warning:** It should be remembered that all local anesthetics are potentially toxic drugs. Therefore, the minimum amount of local anesthetic agent necessary to produce adequate anesthesia and avoid toxic reactions should be used at all times. Moreover, as with other types of drugs, the use of local anesthetics such as Citanest (prilocaine) should be minimal during pregnancy. This, of course, does not exclude the use of local anesthetics at term for obstetrical analgesia. Citanest (prilocaine) has been used effectively for obstetrical analgesia with no adverse effects noted on the fetus, course of labor, or delivery.

**Precautions:** The peridural space can be approached from the thoracic, lumbar and sacral (caudal) regions. It must be kept in mind that these areas contain venous and arterial plexuses and lymph vessels. Further, the close proximity of these regions to the subarachnoid space constitutes an additional hazard of which the anesthesiologist must be constantly aware. Consequently, the technique of peridural anesthesia should be attempted only by skilled individuals. Close familiarity with, and readiness to make use of every known precautionary measure are mandatory. Further, in addition to the accepted procedure for locating the peridural space, a test dose of 5 cc should be administered at least 5 minutes prior to injecting the total required volume.

While desirable in most instances, the application of the test dose cannot be regarded as a completely effective safety measure. The judicious selection of needles of the proper length and bevel is also important; e.g., in the case of the sacral (caudal) approach, it is necessary that the sacral canal be penetrated for a distance of only 1½ to 2 inches. Since it is possible to puncture the dura by this approach, the use of excessively long needles is definitely precluded.

Local anesthetics react with certain metals and cause the release of their respective ions which, if injected, may cause severe local irritation. Adequate precaution should be taken to avoid this type of interaction.

### *Treatment:*

#### *1. Inadvertent subarachnoid injection:*

- a) Resuscitate with oxygen and control blood pressure with vasopressor agents.
- b) Aspirate spinal fluid until 50 cc is removed.

2. Barbiturates may be used prophylactically but offer only a small degree of protection against a lethal dose.

*Side effects and their treatment:*

1. Syncope—Stop injection, recumbent position with legs raised, oxygen, aromatic spirits of ammonia, cold compresses.

2. Hypotension—Stop injection, recumbent position with legs raised, assure adequate ventilation with oxygen. Support circulation with vasopressor if necessary.

3. Apnea—Stop injection, recumbent position, maintain patent airway, artificial respiration with oxygen.

4. Headache and/or backache—Bed rest, analgesic agents as needed. It should be remembered that these side effects most often accompany spinal anesthesia and Citanest (prilocaine) is not recommended for spinal use at this time.

5. Nausea and vomiting—Stop injection, maintain patent airway, prevent aspiration, anti-emetics as needed.

**Methemoglobinemia:** At a dose of 600 mg of Citanest (prilocaine), which is the maximum recommended dose for any anesthetic procedure, methemoglobin formation did occur but was less than 15% of total hemoglobin in all patients studied.

With respect to the clinical symptoms associated with methemoglobinemia, the following statement has been made in textbooks: In general, levels of less than 20 per cent methemoglobin are usually not associated with symptoms. At levels of 20 to 50 per cent fatigue, weakness, dyspnea, tachycardia, headaches, and dizziness may occur. In studies conducted to date no patient in whom the maximum recommended dose of 600 mg of Citanest (prilocaine) was used demonstrated a methemoglobin value in excess of 15% and no clinical symptoms have been observed. Moreover, in clinical studies involving approximately 9000 cases in which Citanest (prilocaine) has been used, only one patient who received a single injection of 900 mg has been reported to have exhibited clinical symptoms of lightheadedness and dizziness may have been related to methemoglobin value in excess of 20%.

**Administration and Dosage:** With the exception of therapeutic nerve blocks, 20-30 ml of Citanest (prilocaine) hydrochloride 1% or 2% and 15-20 ml of Citanest (prilocaine) hydrochloride 3% will usually produce adequate operative anesthesia.

The onset of anesthesia, the duration of anesthesia and the degree of muscular relaxation are proportional to the volume and concentration of local anesthetic used. Thus, an increase in volume and concentration of Citanest (prilocaine) will decrease the onset of anesthesia, prolong the duration of anesthesia, provide a greater degree of muscular relaxation and increase the segmental spread of anesthesia. It should be remembered, however, that increasing the volume and concentration of Citanest (prilocaine) may result in a more profound fall in blood pressure when used in peridural anesthesia. Although the incidence of side effects in clinical trials was quite low, caution should be exercised particularly when employing large volumes and concentrations of Citanest (prilocaine) since the incidence of side effects is directly proportional to the total dose of local anesthetic agent injected.

**Maximum recommended dosage:** Normal Healthy Adults: No more than 600 mg of Citanest (prilocaine) hydrochloride should ever be administered as a single injection, i.e., no more than 8 mg/kg or 4 mg/lb should be given as a single injection. The maximum total dose which may be administered over a period of several hours (e.g., for continuous peridural anesthesia) without side effects is not known as yet. Doses in excess of 2000 mg have been administered over a five-hour period with no toxic symptoms. However, until further data is available we would recommend that doses in excess of 600 mg not be administered at intervals of less than two hours so that one should not exceed a total dose of 1200 mg in a four-hour period.

**Children:** Experience in children under the age of ten (10) is limited. It is extremely difficult to recommend a maximum dose of any drug for children since this varies as a function of age and weight. With respect to Citanest (prilocaine) hydrochloride, 400 mg have been used without toxic effects in children of 10-15 years. However, for children of less than 10 years who have a normal lean body mass and normal body development, we recommend the use of one of the standard pediatric drug formulas (e.g., Clark's rule or Young's rule) to determine the maximum dose. For example, in a child of five years weighing 50 lbs., the dose of Citanest (prilocaine) hydrochloride should not exceed 150-200 mg

when calculated according to Clark's rule or Young's rule. In order to minimize the possibility of toxic reactions in children use of the 1% concentration of Citanest (prilocaine) hydrochloride is recommended.

**Patients with Liver Disease and Debilitated Patients:** The use of any general or local anesthetic agent is undesirable in patients with liver disease or severely debilitated patients. However, for emergency or definitive surgical procedures where a local anesthetic is required, care should be taken to use the lowest dose and concentration of Citanest (prilocaine) hydrochloride necessary to provide adequate anesthesia. It is extremely difficult to recommend a maximum safe dose of any drug for such patients, since this will depend on the degree of liver damage and degree of debilitation. For most anesthetic procedures, it is advisable to use the 1% concentration of Citanest (prilocaine) hydrochloride in order to obtain the minimum dose that will provide adequate anesthesia and thereby avoid possible toxic reactions in patients with liver disease or debilitated patients. In such patients it is probably not advisable to exceed a maximum dose of 400 mg.

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**DEAR DOCTOR:** The Food and Drug Administration has asked us to call your attention to certain advertisements for Mysteclin-F products which the FDA regards as misleading. The main theme of the advertising, which we have stopped, suggests that "almost every candidate for broad-spectrum antibiotic therapy, is a candidate for Mysteclin-F."

We wish to emphasize that those patients selected for tetracycline therapy who are known to be particularly susceptible to candidal superinfection are the potential candidates for Mysteclin-F therapy.

The FDA points out that recent journal advertisements for these products suggested that candidal superinfection is a serious problem with the use of ampicillin. This was not supported by the reference used in the ads. Although the reference cited included the statement that candidal overgrowth may follow ampicillin therapy, the FDA has asked that we point out that the significance of this overgrowth has not been established.

Further, the same ads omitted important warning information relating to precautions and side effects. The nature and extent of the omission are capitalized in the enclosed "Brief Summary".

Sincerely,

SQUITTB.

(NOTE.—This revised "Brief Summary" for use in future medical journal advertising contains additional phrases and items (printed in capital letters) from the official package insert.)

**Contraindications:** History of hypersensitivity to either component.

**Warning:** If renal impairment exists, lower-than-usual doses are indicated to avoid systemic accumulation and possible liver toxicity; on prolonged use, tetracycline serum level determinations may be advisable. Photodynamic reactions, although rare with teracycline, may occur; if they occur, discontinue drug. Advise photosensitive patients to avoid direct sunlight.

**Precautions:** Watch for signs of secondary infection due to nonsusceptible organisms; discontinue drug and/or institute appropriate therapy if this occurs. **SUPERINFECTION OF THE BOWEL BY STAPHYLOCOCCI MAY BE LIFE-THREATENING.** Use of tetracycline, particularly long-term use, BUT ALSO IN USUAL SHORT TREATMENT COURSES, during the LATTER HALF OF GESTATION, NEONATAL PERIOD, AND EARLY CHILDHOOD tooth development may cause discoloration of teeth. **TETRACYCLINE MAY FORM A STABLE CALCIUM COMPLEX IN BONE-FORMING TISSUE WITHOUT HARMFUL EFFECTS REPORTED THUS FAR.** During long-term therapy, perform periodic renal, hepatic, and hematopoietic function studies. Increased intracranial pressure with bulging fontanels has been observed rarely in infants taking therapeutic doses of tetracycline. **USE WITH CAUTION IN PERSONS WITH A HISTORY OF ALLERGY, ASTHMA, HAY FEVER, OR URTICARIA DUE TO GREATER POSSIBILITY OF SENSITIVITY REACTIONS.** CROSS-SENSITIZATION WITH OTHER TETRACYCLINES IS COMMON. IN THE TREATMENT OF GONORRHEA, PATIENTS WITH A SUSPECTED LESION OF SYPHILIS SHOULD HAVE DARK-FIELD EXAMINATIONS BEFORE RECEIVING TETRACYCLINE AND MONTHLY SEROLOGIC TESTS FOR A MINIMUM OF THREE MONTHS.

*Note:* SOME STRAINS OF STAPHYLOCOCCI, STREPTOCOCCI, PNEUMOCOCCI, E. COLI, AND SHIGELLA HAVE SHOWN RESISTANCE TO TETRACYCLINES. MICROORGANISMS THAT HAVE BECOME INSENSITIVE TO ONE TETRACYCLINE INvariably EXHIBIT CROSS-RESISTANCE TO OTHER TETRACYCLINES, AND TETRACYCLINE RESISTANT GRAM NEGATIVE BACILLI MAY SHOW CROSS RESISTANCE TO CHLORAMPHENICOL. THEREFORE, INDICATED LABORATORY STUDIES, INCLUDING SENSITIVITY TESTS, SHOULD BE PERFORMED.

*Side Effects:* ANOREXIA, EPIGASTRIC DISTRESS, NAUSEA, VOMITING, BULKY LOOSE STOOLS, DIARRHEA, STOMATITIS, GLOSSITIS, ENTEROCOLITIS, PROCTITIS, PRUITUS ANI, BLACK HAIRY TONGUE, SORE THROAT, DYSPHAGIA, HOARSENESS, MACULOPAPULAR AND ERYTHEMATOUS RASHES, A RARE CASE OF EXFOLIATIVE DERMATITIS, rarely PHOTOSENSITIVITY, rarely ONYCHOLYSIS AND NAIL DISCOLORATION, DOSE-RELATED BUN RISE, URTICARIA, SERUM SICKNESS-LIKE REACTIONS, ANGIONEUROTIC EDEMA, ANAPHYLAXIS, BULGING FONTANELS IN INFANTS, DENTAL STAINING (see Precautions), TOOTH-ENAMEL HYPOPLASIA IN CHILDREN, ANEMIA, THROMBOCYTOPENIC PURPURA, NEUTROPEIA, EOSINOPHILIA, AND RARELY CHOLESTASIS ASSOCIATED WITH HIGH DOSAGE, URINARY NITROGEN LOSS WHICH MAY RESULT IN NEGATIVE NITROGEN BALANCE AND INCREASED SODIUM EXCRETION, DELAYED BLOOD COAGULATION, AND DEVELOPMENT OF PEPTIC ULCERS AND BLEEDING IN UREMIC PATIENTS. IF ALLERGIC REACTIONS OCCUR, OR IF AN INDIVIDUAL IDIOSYNCRASY APPEARS, TETRACYCLINE THERAPY SHOULD BE DISCONTINUED.

ORGANON, INC.,  
West Orange, N.J., October 27, 1967.

DEAR DOCTOR: The Food and Drug Administration has requested that we call your attention to the monographs for Cortrophin® Gel, Cortrophin® Zinc, Hexadrol® Phosphat Injection and Hexadrol® Tablets and Elixir in the current *Physicians Desk Reference*. The FDA considers these monographs to be incomplete in presenting necessary information for the safe and effective use of these drugs, and, therefore, potentially misleading.

To provide you with the necessary information, we enclose revised monographs for insertion in your *PDR*. The nature and extent of the additions and other revisions in the enclosed monographs are emphasized by the use of italics.

Sincerely yours,

JOSEPH D. CUONO, M.D.,  
*Director, Professional Services.*

(NOTE.—Prescribing information for Cortrophin® Gel, Cortrophin® Zinc, Hexadrol® and Hexadrol® Phosphate Injection, which appears on pages 898-899 of your 1967 *PDR*, has been revised and is completely replaced by the following. The nature and extent of the additions and other revisions in the monographs are emphasized by use of italics.)

ORGANON, INC., WEST ORANGE, N.J.

#### PURIFIED CORTROPHIN® GEL

#### Repository Corticotropin Injection U.S.P.

Purified Cortrophin Gel is purified corticotropin (ACTH) in a sterile solution of gelatin for prolonged activity. It is supplied in two strengths: 40 U.S.P. Units and 80 U.S.P. Units per cc. Each cc. of each strength also contains 0.5% phenol (preservative), 15.0% gelatin, pH adjusted with HCl. This product requires fewer injections per day than aqueous corticotropin preparations to maintain adrenocortotropic activity. It is solid at or below room temperature; before use, the gel should be liquefied by holding the vial under warm tap water. It should be injected subcutaneously or intramuscularly, never intravenously; a 20 or 21-gauge needle should be used. Injection sites should be alternated, and brief, firm pressure should be applied on the site after each injection.

**Properties**—This product offers prolonged ACTH activity. It stimulates the adrenals to an increased production of all the adrenocortical hormones. Three types of adrenal hormones are produced in this way: compound F-like hormones

(cortisone-like), which are the most abundant; desoxycorticosterone-like hormones; and the adrenal androgens. The production of compound F-like hormones is clinically the most significant, for these particular steroids are the ones that produce striking clinical response in so many diseases, and which enable the tissues and the body as a whole to meet serious stress. Adequate therapy usually produces the following desirable general changes: Temperature, if elevated, usually returns to normal within 6 to 18 hours. Pain is abolished within a short time and becomes an index of the reversibility of the disease under treatment. Patients develop a sense of well-being and of mental activity bordering on euphoria. Fibroblastic proliferation and inflammatory processes are blocked.

#### SPECIAL PRECAUTIONS WITH ADRENOCORTICOTROPIC THERAPY

*This product functions by stimulating the production of steroid hormones by the adrenal cortices, and in this manner influences protein and carbohydrate metabolism, alters the metabolism of electrolytes with retention of sodium and excretion of potassium. In this same manner the steroid hormones of the adrenal cortices induce atrophy of the thymus and produce an increase in antihyaluronidase activity. Prolonged or excessive stimulation of the adrenals may produce undesirable effects, and for this reason each patient should be carefully observed to determine his response.*

1. *Edema*—With large doses or during prolonged use, sodium retention with intake, giving a diuretic, or by temporarily discontinuing therapy until diuresis results. If potassium deficiency with muscular weakness or edema occurs, supplemental potassium should be given: 1 Gm potassium citrate or chloride given orally three times a day.

2. *Temperature and Infection*—This product may mask signs of concomitant serious infections and therapy should be discontinued temporarily in order to permit diagnosis of the infection. Therapy may be resumed if warranted after specific therapy for the infection has been given.

3. *Disturbed Psyche*—If psychotic changes appear, these isolated cases should be treated by reducing or discontinuing dosage of corticotropin and the use of sedatives should begin.

4. *Hyperglycemia and Glycosuria*—Excessive dosage may increase the blood sugar and glycosuria may occur; this can be eliminated by reduction of dosage or cessation of therapy (see contraindications for diabetes below).

5. *Hypertension*—In certain individuals a marked increase in blood pressure may occur, and in these instances the dose should be reduced or eliminated.

6. *Acne and Hirsutism*—Prolonger therapy may cause overstimulation of androgenic hormone secretion which may induce these symptoms in some women; and these conditions may be controlled by suitable reduction in dosage. In severe cases, therapy may have to be discontinued.

7. *Hypersensitivity*—Susceptible individuals may become sensitized to traces of protein that accompany corticotropin so that subsequent injections given after intervals of several days may give rise to hypersensitivity phenomena. Therefore, patients who have previously been treated with corticotropin should be tested for sensitivity, and sensitive individuals should be desensitized before treatment is begun.

**Test of Adrenocortical Activity**—One of the requisites to successful corticotropin therapy is a functioning adrenal cortex. The functional capacity of the adrenal conditions clinical response. A reduction in the number of circulating eosinophils is considered to reflect increased secretion of adrenal steroids and indicates a positive response to corticotropin. Normal subjects respond to the injection of adequate doses of ACTH with at least a 50 per cent fall in circulating eosinophils. The test (known as the Thorn test) is applied in the diagnosis of Addison's disease, as a test of adrenal reserve pre- and post-operatively, to determine the patient's ability to react to stress, and to differentiate between panhypopituitarism, functional hypopituitarism and Addison's disease. In hypopituitarism, where hypofunction lies in the hypophysis, reaction to the test is positive. In Addison's disease, where the deficiency resides in the adrenals, the response is negative.

**Dosage Considerations**—Because functional capacity of the adrenal varies with the patient, the dose must be individualized, the aim being to obtain a therapeutic effect with minimal dosage and minimal metabolic changes. In severe cases, it may be advisable to initiate treatment with aqueous corticotropin (not

*the gel form) by the intravenous route, changing to this product for maintenance therapy.*

Although the dosage must be individualized to the patient and the disturbance being treated, the initial dose requirements will probably be in the vicinity of 40 to 60 units of corticotropin per day. Ordinarily, where the preparation is to be used continuously, or for prolonged periods, the daily dose should not be over 20 units and usually less. It is preferable to maintain the dosage of ACTH at a level that will avoid undesirable side effects even though this dosage be insufficient to produce complete relief of the clinical disorder under treatment. Minimum dosage levels should be used in all cases of prolonged therapy. The amount required per day governs the frequency of injections; for example, if 60 units are required, the amount is given as two equally divided doses, if less than 40 units is required, the dose is administered as a single daily injection.

It is best to decrease the dosage as quickly as possible after the desired response is obtained. First, the dose is reduced to about three-fourths that needed initially; this is continued for about a week to determine its adequacy. The dose is again reduced step-wise by one-fourth every 5 to 7 days until the lowest maintenance dose is established. After about a week, this dose is administered every other day. If improvement is maintained, then the interval is lengthened to every three days. The general principle is to give the smallest dose in the longest interval. If the dose needed for full relief produces significant side effects it should be reduced and the physician should content himself with less than full suppression of the disease being treated.

#### CONTRAINDICATIONS

1. Tuberculosis—Active or latent tuberculosis is a definite contraindication for prolonged therapy.

2. Congestive Heart Failure and Hypertension—Corticotropin therapy, through its tendency to induce electrolyte and fluid retention, is undesirable for these conditions.

3. Psychotic and Psychopathic Personalities—Corticotropin therapy may precipitate undesired incidents, and hence persons with psychopathic personalities should usually not receive the drug until further studies have been made.

4. Diabetes Mellitus—*Corticotropin therapy may increase the blood sugar levels especially of controlled diabetics or latent diabetics so that glycosuria may result. This may be controlled by increasing the insulin dosage and adjustment of diet, and in most cases discontinuance of the corticotropin brings blood sugar levels and insulin requirements back to pretreatment values.*

5. Chronic Nephritis—It is essential that the patient be able to eliminate excess water which tends to be retained on corticotropin therapy, due to sodium reten-tion. The inability of the nephrotic to eliminate excess fluid requires caution.

6. Cushing's syndrome—*This disease is due to excessive function of the adrenal cortex or to tumors, and corticotropin therapy is contraindicated.*

7. Addison's Disease—Corticotropin therapy is ineffective in the absence of adrenal tissue.

8. Thrombophlebitis—Since ACTH therapy tends to increase the thrombo-philic tendency, patients, particularly those confined to bed or chair, should be watched for signs of phlebothrombosis, which should be treated with anticoagulant therapy before and during the ACTH therapy.

#### INDICATIONS

*The following dosage recommendations for this product to be administered subcutaneously or intramuscularly are intended as suggestions for initial therapy, and thereafter the dosage must be adjusted to the individual needs of the patient.*

Rheumatoid Arthritis—The initial dose is 60 units once a day; for severe cases, 30 to 40 units every 12 hours. If clinical response is not obtained after several days, increase dose to 80 units every 24 hours. After remission occurs, gradually reduce dose as described under Dosage Considerations.

Acute Rheumatic Fever—In young children 40 units per day as one injection; if acutely ill, 30 units every 12 hours. For older children, 60 units once a day. Full treatment for 4 days, then gradual tapering off and treatment discontinued.

Acute Lupus Erythematosus—The initial dose is 60 units every 24 hours. The patient should be maintained on the effective dose for 2 to 3 weeks at which time the dose should be reduced to the minimum maintenance level. These patients must be carefully observed for edema with cardiac and nephritic involvement. Low sodium diet and increased potassium intake is advisable.

*Severe Hay Fever*—40 to 60 units once a day. Treatment period averages 3 to 5 days with a gradual tapering off afterward.

*Drug Sensitivities and Contact Dermatitis*—A dosage of 80 units once a day for 2 days will usually control symptoms; dosage reduced gradually and then discontinued.

*Urticaria*—A dosage of 80 units once a day for 1 to 3 days, with gradual tapering off. Some cases may require maintenance of 10 to 40 units every 1 to 3 days.

*Acute Inflammatory Diseases of the Eye*—In iritis, keratitis, uveitis, chorioiditis, optic neuritis, sympathetic ophthalmia, acute secondary glaucoma, and conjunctivitis, 40 to 60 units are needed once a day until the eye lesion has fully healed. After gradual tapering off of dosage, treatment can be discontinued for most patients; in some who have had the disease for an extended period, maintenance therapy of 10 to 40 units once a day or every 2 to 3 days may be required. Attempts should be made periodically to discontinue treatment.

*Acute Inflammatory Diseases of the Skin*—In acute psoriasis, exfoliative dermatitis and severe pemphigus, from 40 to 60 units a day for a short period, with gradual tapering off. Most patients will require maintenance therapy of from 10 to 40 units once daily or every 2 to 3 days, unless the cause is known and eliminated.

*Ulcerative Colitis*—For less severe cases, 40 units once daily; for severe cases, 60 to 80 units daily until mucosa appears relatively normal. Maintenance dose of 10 to 40 units every 1 to 3 days may be required in chronic cases.

*Acute Gouty Arthritis*—Emergency treatment of 80 units per day. Less ill patients should receive 40 to 60 units once daily. Treatment is repeated until symptoms subside—usually after 1 to 3 injections. Other therapy for gout should be concurrently administered. ACT H therapy is usually not required.

*Congenital Idiopathic Hypoglycemia*—20 to 40 units once a day for small children. Full treatment extends to at least 10 days after adequate control. Maintenance dose of 10 to 20 units every 1 to 3 days after patient is well under control.

*Alcoholism (acute delirium tremens)*—40 units twice a day until symptoms have disappeared (usually within 24-36 hours.) When symptoms are controlled, reduce dosage to 20 units twice a day for 2 to 3 days, then 20 units per day for 2 to 3 days; finally 20 units three times a week for 2 to 4 weeks. ACT H therapy is not recommended for Korsakoff's psychosis.

*Packages*—This product retains potency for at least three years. It should be kept in a refrigerator. Available in 5-cc vials, in two strengths: 40 U.S.P. units and 80 U.S.P. units of purified corticotropin (ACTH) per cc. and in 1-cc ampuls containing 40 U.S.P. units.

**CAUTION:** Federal law prohibits dispensing without prescription.

#### CORTROPIIN "ZINC"

#### Sterile Corticotropin Zinc Hydroxide Suspension U.S.P.

*Composition*—An aqueous suspension of purified corticotropin (ACTH) with alpha zinc hydroxide for repository action. It is available as 40 U.S.P. units of corticotropin 1<1 (1.0 mg. of zinc content per cc), which provides therapeutic ACTH activity for a period of from one to three days, depending upon individual patient requirements. Each cc also contains: 1.0% benzyl alcohol (preservative) and made isotonic with NaCl, pH adjusted with HCl and NaOH. This is a fine aqueous suspension which flows readily through a 24-26 hypodermic needle. It should be given intramuscularly to avoid any possible local reaction.

*Properties*—This product supplies pituitary corticotropin in a form which provides sustained action of the hormone, causing the adrenal cortex to release its essential steroids in physiological proportions over a longer period of time than would be the case with corticotropin in equal amounts in other forms. This period of activity ranges from 1 to 3 days depending upon the patient's requirements and upon the strength administered. The response is conditioned by the functional capacity of the adrenal cortex; a highly active gland would respond dramatically, while an inactive adrenal cortex would respond less, particularly at first. This response takes the form of an outpouring of three types of adrenal hormones: compound-F-like hormones which are the most abundant; desoxycorticosterone-like hormones; and the adrenal androgens. The production of compound-F-like hormones is clinically the most significant, for it is this aspect of therapy that promotes striking clinical response in so many diseases, and which enables the tissues and the body as a whole to meet serious stress.

Adequate therapy usually produces the following desirable general changes: Temperature, if elevated, usually returns to normal within 6 to 18 hours. Pain is abolished within a short time and becomes an index of the reversibility of the disease under treatment. Patients develop a sense of well-being and of mental activity bordering on euphoria. Fibroblastic proliferation and inflammatory processes are blocked.

**Test of Adrenocortical Activity**—One of the requisites to successful corticotropin therapy is a functioning adrenal cortex. The functional capacity of the adrenal conditions clinical response. A reduction in the number of circulating eosinophils is considered to reflect increased secretion of adrenal steroids and indicates a positive response to corticotropin. Normal subjects respond to an adequate dose with at least a 50 per cent fall in circulating eosinophils. This test (known as the Thorn test) is applied in the diagnosis of Addison's disease, as a test of adrenal reserve pre- and post-operatively, to determine the patient's ability to react to stress, and to differentiate between panhypopituitarism, functional hypopituitarism and Addison's disease, in hypopituitarism, where hypofunction lies in the hypophysis, reaction to the test is positive. In Addison's disease, where the deficiency resides in the adrenals, the response is negative.

**Dosage Considerations**—As with corticotropin in gelatin and aqueous corticotropin, the dosage must be individualized to the requirements of the particular patient and the disturbance being treated. Because of the enhanced and prolonged activity, fewer injections are required.

*In general, it seems practical to gain initial control of symptoms with an injection of 40 U.S.P. units, (in more severe cases, 60 units) daily. Once symptoms have been controlled, the interval between injections should be increased to 48 hours and then to 72 hours. Thereafter, if symptoms are still controlled, the dose per injection should then be reduced. For maintenance therapy, 20 U.S.P. units (or even less) daily to twice weekly may suffice. The general principle is to give the smallest dose in the longest interval. If the dose needed for full relief produces significant side effects it should be reduced and the physician should content himself with less than full suppression of the disease being treated.*

*In the treatment of acute diseases, physicians who have had experience with corticotropin-in-gelatin preparations should consider the following dosage suggestions. In view of the fact that this product has an action which is prolonged for at least 24 hours, and in most cases for a longer period, and its activity is at least as great as that of the gel preparations, the initial dose should be the same as that employed per single dose of the gelatin preparation; however, this dose should be given only once in the 24-hour period, and seldom in more than 60 units. The interval between injections should be extended to 48 hours and to 72 hours as soon as expedient, and the dose per injection should then be reduced, as described in the foregoing paragraph.*

*When immediate therapeutic results are mandatory, as in acute status asthmaticus, it may be desirable for the physician to administer aqueous corticotropin initially by the intravenous route and at the same time to give the first dose of this product intramuscularly into the deltoid muscle. (This product must not be given intravenously.) Once the initial control of the disease have been effected, the patient may be satisfactorily maintained intramuscularly.*

*Withdrawal of therapy results temporarily in relative adrenocortical deficiency because the patient's own production of ACTH has been suppressed. Withdrawal should be gradual to prevent a rebound reaction of relative deficiency. It is noteworthy, however, that this period of inactivity is usually shorter than that following cortisone therapy.*

#### INDICATIONS

The indications for this product are the same as those for other corticotropin preparations. In general the following dosage schedules have been employed successfully:

*In dermatologic disorders (atopic dermatitis, schorrhie psoriasis, pemphigus vulgaris), dosage has been 40 units every two to four days. Maintenance treatment has in some cases been achieved with 40 units once a week.*

*In rheumatoid arthritis, dosage in general has been 40 to 60 units per day until control is achieved, then reduced to 20 to 40 units every other day for maintenance. It has been possible in some cases to reduce the dosage even further.*

*In drug sensitivities, dosage has been 20 to 40 units per day until symptoms are controlled. This dosage has also been employed in the treatment of poison ivy.*

*In acute lupus erythematosus, dosage has averaged 40 to 60 units or more per*

day to gain control of the symptoms with maintenance treatment possible in some cases with 20 units every other day. However, many of these patients have relatively high dosage requirements, even during maintenance treatment, and in these cases the sustained action seems to be particularly beneficial to satisfactory control of the disease.

In bronchial asthma, including status asthmaticus, 60 units a day were required for control, and 40 units twice a week has in some instances provided successful maintenance.

In polyarteritis and periarteritis nodosa, the initial dosage suggested is 40 units per day, maintenance may be achieved with 40 units twice a week.

In pulmonary emphysema, initial dosage has been 60 units per day, reduced to 20 units per day or every other day for maintenance.

These dosages are, of course, only gauges for the physician to follow. As with other corticotropin preparations, either the gel-form or aqueous, the dosage must be adjusted to the needs of the particular patient being treated.

**Contraindications**—The use of corticotropin is contraindicated in Addison's disease. Tuberculosis, active, latent or questionably healed, herpes simplex of the eye, and acute psychoses are usually absolute contraindications. Peptic ulcer, psychotic tendencies, diverticulitis, fresh intestinal anastomoses, thromboembolic tendencies, local or systemic infections including fungal and exanthematous diseases, osteoporosis, renal insufficiency, congestive heart failure and pregnancy (except in severe disease) are relative contraindications.

This product should not be used in patients with a history of previous reactions to any form of corticotropin or who are known to be allergic to products of porcine origin.

**Precautions and Side Effects**—This product functions by stimulating the production of steroid hormones by the adrenal cortices, and in this manner influences protein and carbohydrate metabolism. It also alters the metabolism of electrolytes with retention of sodium and excretion of potassium. Should sodium retention and edema occur this may be controlled by restricting sodium intake, giving a diuretic or by temporarily discontinuing therapy until diuresis occurs. If potassium deficiency with muscular weakness occurs supplemental potassium should be given: 1 Gm. potassium citrate or chloride orally three times a day. Periodic determinations of serum potassium during prolonged therapy is advised. In this same manner the steroid hormones of the adrenal cortices induce atrophy of the thymus and produce an increase in antihyaluronidase activity. Because the action of this product is enhanced and prolonged as compared with other corticotropin preparations, the possibility of overdosage symptoms must be borne in mind.

Corticotropin will produce the same type of side effects as corticosteroids and these include: Cushing-like syndrome, purpura or petechiae, electrolyte imbalance, insomnia, osteoporosis, spontaneous fractures, peptic ulcer, euphoria, psychic disturbances, menstrual irregularities, weight changes, hyperglycemia, hypertension, edema, bloating or gastric distress, aseptic necrosis of the hip, protein depletion, pancreatitis, increased intracranial pressure, convulsions, and hirsutism. Vascular changes such as polyarteritis nodosa or an increased tendency for thrombophlebitis have been reported. The incidence, type and severity of untoward reactions is usually related to the size of the dose and duration of therapy. For example prolonged use of corticotropin may also cause growth suppression (reversible on withdrawal) in children, delayed wound healing, or posterior subcapsular cataracts in adults.

Susceptible individuals may become sensitized to traces of protein that accompany corticotropin so that subsequent injections given after intervals of several days may give rise to hypersensitivity phenomena ranging from mild urticaria to anaphylactic shock. The first sign of developing hypersensitivity may be localized itching or wheal formation at the injection site. This product should not be used in patients with a history of previous reactions to any form of corticotropin or who are known to be allergic to products of porcine origin.

It may be used as adjuvant therapy in certain infectious diseases providing such infections are adequately controlled by appropriate antibiotics or chemotherapeutic agents. It must be remembered that the anti-inflammatory effects of corticotropin may mask signs of infection and such patients should be carefully observed. While average doses will usually not increase insulin requirements in controlled diabetics, when the drug is used in such patients, they should be observed closely for evidences of increased hyperglycemia or glycosuria. Periodic determinations of blood sugar during prolonged therapy is advised.

Packages—This product should be refrigerated. Available in 5-cc vials containing 40 U.S.P. units of corticotropin (ACTH) per cc.

Caution: Federal law prohibits dispensing without prescription.

#### HEXDROL

##### *Dexamethasone 'Organon'*

Description and Action—Hexadrol (dexamethasone 'Organon') is an analogue of prednisolone. Its spectrum of anti-inflammatory activity is similar to other corticosteroids but it is clinically effective in much lower doses. Chemically it is 9-alpha-fluoro, 16-alpha-methyl prednisolone.

Indications—It may be used singly or as adjuvant therapy in a wide variety of clinical states known to be responsive to steroid therapy. Such conditions include rheumatic and other collagen diseases, hypersensitivity states, certain inflammatory eye diseases, blood dyscrasias, certain neoplastic diseases, and other miscellaneous disorders.

Contraindications—Tuberculosis, active, latent or questionably healed, herpes simplex of the eye and acute psychosis are usually absolute contraindications. Peptic ulcer, psychotic tendencies, diverticulitis, fresh intestinal anastomoses, thromboembolic tendencies, local or systemic infections including fungal and exanthematous diseases, osteoporosis, renal insufficiency are relative contraindications. Corticosteroids have produced teratogenic effects in animal fetuses and for this reason dexamethasone should not be used in pregnant women except in severe disease. In the event that corticosteroids must be used in pregnant women, newborn infants should be carefully observed for possible postnatal hypoadrenalinism.

Precautions and Side Effects—All corticosteroids, including dexamethasone, produce the same type of side effects and these include: Cushing-like syndrome, purpura or petechiae, electrolyte imbalance, insomnia, osteoporosis, spontaneous fractures, negative nitrogen balance, peptic ulcer, euphoria, psychic disturbances, menstrual irregularities, weight changes, hyperglycemia, hypertension, edema, bloating or gastric distress, aseptic necrosis of the hip or humerus, and hirsutism. Vascular changes such as polyarteritis nodosa or an increased tendency for thrombophlebitis have been reported. Ulcerative esophagitis and acute pancreatitis have occurred during, and may be related to, corticosteroid therapy. Some corticosteroids such as the fluoro analogues of prednisolone appear to exert a relatively greater muscle wasting effect. The incidence, type and severity of untoward reactions is usually related to the size of the dose and duration of therapy. For example *prolonged use of corticosteroids may also cause growth suppression (reversible on withdrawal) in children, delayed wound healing, or posterior subcapsular cataracts in adults.* Because of the greatly enhanced anti-inflammatory activity of dexamethasone, lower doses can be used thus preventing or minimizing abnormal salt and water retention or potassium loss. *Periodic serum potassium determinations are advised during prolonged therapy.*

*It may be used as adjuvant therapy in certain infectious diseases providing such infections are adequately controlled by appropriate antibiotics or chemotherapeutic agents. It must be remembered that the anti-inflammatory effects of corticosteroids may mask signs of infection and such patients should be carefully observed.* While average doses will usually not increase insulin requirements in controlled diabetics, when the drug is used in such patients, they should be observed closely for evidences of increased hyperglycemia or glycosuria. Periodic determinations of blood sugar during prolonged therapy are advised.

It is safest to assume that prolonged therapy will result in depression of adrenocortical function. For this reason the drug should be withdrawn gradually when treatment is to be discontinued. *It may be advisable to administer ACT II during this period to hasten the return of normal function. Should the patient be subjected to surgery, severe trauma, or shock within one year following withdrawal it may be advisable to give a temporary course of corticosteroid therapy.* Dexamethasone is not the drug of choice in adrenal insufficiency.

*Dosage—Rheumatoid Arthritis:* It will effectively suppress the inflammatory reaction seen in rheumatic disorders generally within 24-48 hours. Improvement is characterized by relief of pain, decrease in redness, pain, swelling, stiffness and a sense of well-being. So predictable is the response of this disorder to steroid therapy, assuming adequate dosage, that if no response is noted within seven days, the diagnosis should be questioned.

In general an initial daily dose of 1.5 to 3.0 mg. will produce a good clinical response although a few patients may require more. The effective minimal main-

tenance dose should then be determined for each patient and this will usually range between 0.75 and 1.5 mg. per day. Dosage titration is easily accomplished by decreasing the daily dose by 0.25 mg. or 0.375 mg. every three days or so. The use of a single daily dose may prove effective in certain patients and may be worthy of trial initially. However, if the response is not satisfactory the daily drug requirement should then be given in divided doses.

Because of the spontaneous remissions seen in this disease it may be advisable from time to time to discontinue therapy to evaluate this point, particularly in patients whose daily drug requirements are low. It should be emphasized that this agent is most effective when used in conjunction with other standard measures such as rest, physiotherapy, orthopedic corrections, etc.

**Acute Rheumatic Fever**—It can be expected to exert the same type and degree of beneficial effects noted with other corticosteroids in the treatment of this disease. Unlike earlier corticosteroids, it has the added advantage that salt and water retention are rarely observed, at least at the lower dosage levels. The true role of these agents in preventing valvular damage has yet to be determined. High doses are usually required to bring this disease under control and initially these may range from 7.5 to 10 mg. daily. As symptoms improve, dosage should be decreased gradually until a satisfactory maintenance level is reached.

**Hypersensitivity States**—Allergic diseases such as bronchial asthma, angioneurotic edema, allergic dermatoses, allergic purpura, certain drug reactions, transfusion reactions, etc. constitute another group of disorders responsive to corticosteroid therapy. In general a single daily dose will usually provide adequate symptomatic control. Sufficiently high doses should be given initially to provide relief and these may range from 3.0 to 6.0 mg. per day. When long-term therapy is required, the effective minimal dose should be determined for each patient by gradually reducing dosage by 0.25 mg. to 0.375 mg. every second or third day.

For relatively minor conditions such as intractable hay fever or allergic rhinitis, the use of this agent may usually be discontinued after 10 to 14 days. Standard antiallergic therapy should be tried initially with corticosteroid supplementation only if required.

**Inflammatory Eye Diseases**—Ocular diseases which are known to respond to such therapy include: iritis, iridocyclitis, urethritis, choroiditis and chorioretinitis. In iritis or iridocyclitis topical treatment should be tried before restoring to systemic use. The drug is contraindicated in herpes simplex and herpes keratitis.

Beginning doses range from 3.0 to 6.0 mg. per day. When symptoms are satisfactorily controlled, dosage should be decreased by 0.50 to 0.75 mg. daily until a satisfactory maintenance dose is achieved. In acute or self-limited conditions, corticosteroids should be discontinued at the earliest possible moment.

**Skin Disorders**—Dermatitis of the atopic, contact, exfoliative, or drug reaction types respond rapidly and favorably, a single daily dose usually providing symptomatic relief. Skin diseases of a more serious impact such as pemphigus vulgaris and mycosis fungoidea may also respond to corticosteroid therapy. The skin lesions associated with collagen diseases such as lupus erythematosus, scleroderma, and dermatomyositis do not require treatment but may respond favorably to courses of corticosteroid therapy being given for the underlying disease. Dosage requirements for these various skin disorders should be based on the degree of involvement and severity of the underlying disease. Minor afflictions require therapy for a few days or weeks at most while the more serious ones may demand continuous treatment. In general initial doses range from 3.0 to 6.0 mg. per day with gradual reductions down to a satisfactory maintenance level. Higher daily drug requirements should be given in divided doses.

Dosage recommendations for the treatment of pemphigus, scleroderma, and mycosis fungoidea vary considerably and the interested physician is advised to consult the latest literature for suggested therapeutic regimens.

**Adrenogenital Syndrome**—It will effectively suppress adrenocortical hypersecretion with prompt decreases in urinary 17-ketosteroid levels. Optimal maintenance doses must be determined for each individual as reflected by continuation of normal urinary 17-ketosteroid levels. A dose of 0.75 to 1.5 mg. daily will usually provide the desired effect.

**Bursitis**—Soft tissue inflammations such as bursitis, synovitis, and tenosynovitis will respond favorably to corticosteroids. Initial daily doses of 1.5 to 3.0 mg. will provide a rather prompt and satisfactory result and short courses of therapy usually suffice. The majority of patients will respond satisfactorily to a single daily dose.

*Miscellaneous Diseases—The anti-inflammatory corticosteroids may provide a measure of relief in certain other diseases such as: pulmonary fibrosis, pulmonary emphysema, lupus erythematosus, nephrosis, ulcerative colitis, idiopathic thrombocytopenic purpura, and may provide a temporary palliative effect in lymphatic leukemia and lymphomas. It is contraindicated in metastatic carcinoma.*

*Dosage requirements for the above indications must be individualized since most of these diseases have a serious, if not greater prognosis, and vigorous therapy may be justified. The use of high doses will increase the incidence of undesirable side effects. If the risk is accepted, the patient must be carefully observed for their occurrence and treated accordingly.*

As with all potent drugs the dosage of corticosteroids should be individualized. The best dose is the smallest dose which will produce adequate but not necessarily complete relief of symptoms. Higher doses or prolonged periods of therapy tend to produce an increased incidence of side effects and this risk must be balanced against anticipated benefits in every instances. Where large doses are required the patient should be carefully watched for the appearance of the classical signs of overdosage when it may become necessary to decrease the dose or stop therapy.

Corticosteroids are usually given in divided doses. Clinical studies, however, have convincingly demonstrated that a single daily dose is effective for the majority of patients suffering from hypersensitivity states, dermatoses, barsitis or other mild connective tissue diseases, etc. While the response has been less striking in rheumatoid arthritis the incidence of effective control is sufficiently high to make this regimen worthy of trial. Single doses are best given in the morning unless clinical reasons dictate an evening dose.

It is advisable, when discontinuing corticosteroid therapy, to reduce dosage gradually and not abruptly. The administration of ACT II during the withdrawal period may help to accelerate the return of normal adrenocortical function.

Patients currently being treated with other corticosteroids may be transferred conveniently to this agent using the following dosage equivalents:

0.75 dexamethasone equivalent to:

- 25 mg. cortisone.
- 20 mg. hydrocortisone
- 5 mg. prednisone or prednisolone.
- 4 mg. methylprednisolone
- 4 mg. triamcinolone.

**Caution:** Federal law prohibits dispensing without prescription.

**Supplied:**

- 0.50 mg. tablets (yellow, scored), bottles of 30 and 500.
- 0.75 mg. tablets (white, scored), bottles of 100 and 500.
- 1.5 mg. tablets (peach, scored), bottles of 50.
- 0.50 mg./5 ml. elixir (alcohol 5%), bottles of 120 ml.

#### HEXDROL® PHOSPHATE INJECTION

(Dexamethasone Sodium Phosphate, N.F.)

**Description—**Hexadrol phosphate injection (dexamethasone sodium phosphate N.F.) is a water-soluble inorganic ester of dexamethasone which produces a rapid response even when injected intramuscularly. Chemically it is 9-alpha-fluoro, 16-alpha-methyl prednisolone 21-phosphate.

Each cubic centimeter contains:

Dexamethasone sodium phosphate, N.F. -----	4.0 mg.
Sodium Bisulphite U.S.P. -----	3.5 mg.
Sodium Citrate U.S.P. -----	10.0 mg.
Sodium Chloride U.S.P. -----	3.2 mg.
Disodium ethylene diamine tetra-acetate -----	0.1 mg.
Methylparaben U.S.P. -----	0.85 mg.
Propylparaben U.S.P. -----	0.15 mg.
Sodium hydroxide U.S.P. q.s. -----	to pH 7.7.
Water for Injection U.S.P. q.s. -----	1.0 cc.

**Action and Uses—**Dexamethasone sodium phosphate N.F. exhibits the intrinsic properties and hormonal effects of the parent substance and other corticosteroids. When administered intravenously, intramuscularly, intrasynovially or locally it

is an effective anti-inflammatory and anti-allergic agent. Because it is highly soluble, speed of absorption following intramuscular injection is almost as rapid as that following intravenous injection.

Since this product is intended for emergency, short-term or local therapy the pronounced hormonal effects associated with long-term therapy usually will not be seen. It is important, however, to watch for any untoward effect when administering a potent agent such as this. Local injections of therapeutic doses into joints or soft tissues are usually well-tolerated and significant systemic hormonal effects are unlikely if injections are few in number or are given at infrequent intervals.

When this product is given intravenously or intramuscularly it is useful in the following conditions:

1. Hypersensitivity reactions such as:

- (a) Anaphylactic reactions
- (b) Drug reactions
- (c) Status asthmaticus
- (d) Transfusion reactions
- (e) Severe urticaria
- (f) Laryngeal edema
- (g) Acute dermatosea
- (h) Severe reaction to insect bites

2. Acute or relative adrenal insufficiency:

- (a) Medical
- (b) Surgical
- (c) Iatrogenic

3. Shock not responding to conventional therapy.

4. Overwhelming infections with severe toxicity.

5. To initiate therapy in:

- (a) Acute rheumatic fever
- (b) Acute disseminated lupus erythematosus.
- (c) Acute gout

In treating anaphylactic shock or other severe allergic reactions norepinephrine or epinephrine should be used initially together with other accepted procedures. This may be followed by the parenteral administration of this corticoid to provide a more prolonged effect.

Patients who have received prolonged corticoid therapy may develop a state of relative adrenal insufficiency which may persist for a year or more following cessation of therapy. If such patients suffer sudden stress such as trauma, shock, surgery, overwhelming sepsis etc., reinstitution of corticoid therapy during this period may be indicated. This product may be employed for emergency use in these patients. However, because dexamethasone sodium phosphate N.F. lacks significant mineralocorticoid activity supplemental therapy with salt and a salt-retaining steroid such as desoxycorticosterone is required when it is used for the treatment of adrenal insufficiency. Because of the supplemental therapy required, dexamethasone is not the drug of choice in the treatment of adrenal insufficiency.

It may prove lifesaving in critically ill patients suffering from severe overwhelming infections for which specific antibiotic therapy is available. It may permit survival until the antibiotic has had time to take effect. Since corticoids mask the classical signs of infection their use in such cases must be undertaken with the greatest caution. Bacteriological studies and adequate antibiotic therapy must be started before the first dose of this corticoid and its use should be discontinued as soon as possible and at least 3 days before antibiotic therapy is stopped.

Surgical infections requiring corrective surgery should be performed as soon as possible. Clinical improvement following steroid therapy is not an indication to postpone surgery. Increased doses of antibiotic may be indicated while the steroid is being given.

When given intrasynovially or locally into soft tissue sites this product may provide relief of symptoms in:

- (a) Rheumatoid arthritis.
- (b) Acute gouty arthritis.
- (c) Traumatic arthritis.
- (d) Osteoarthritis.
- (e) Bursitis.
- (f) Fibrositis.
- (g) Strains and sprains.
- (h) Ganglia.

- (i) Tendinitis.
- (j) Localized myositis
- (k) Heloma.

**Contraindications**—Tuberculosis, active, latent or questionably healed, herpes simplex of the eye and acute psychosis are usually absolute contraindications. Infectious arthritis is also an absolute contraindication to intra-articular injection. Peptic ulcer, psychotic tendencies, diverticulitis, fresh intestinal anastomoses, thromboembolic tendencies, local or systemic infections including fungal and exanthematous diseases, osteoporosis, renal insufficiency are relative contraindications. Corticosteroids have produced teratogenic effects in animal fetuses and for this reason dexamethasone should not be used in pregnant women except in severe disease. In the event that corticosteroids must be used in pregnant women newborn infants should be carefully observed for possible postnatal hypoadrenalinism.

**Precautions and Side Effects**—Hexadrol phosphate injection (dexamethasone sodium phosphate N.F.) is usually given for short periods of time and the known signs of corticoid overdosage are rarely seen. The appearance and nature of untoward effects depends largely on dosage, duration of treatment, and route of administration. *Faintness, weakness, nausea, dyspnea, weight gain, increased appetite and mental stimulation have been reported as immediate or short-term side effects following its parenteral use.* Untoward systemic hormonal effects from the intrasynovial or soft tissue injection of this agent are not anticipated when injections are few in number or are given at infrequent intervals.

All corticosteroids, including dexamethasone, produce the same type of side effects and these include: Cushing-like syndrome, purpura or petechiae, electrolyte imbalance, insomnia, osteoporosis, spontaneous fractures, negative nitrogen balance, peptic ulcer, euphoria, psychic disturbances, menstrual irregularities, weight changes, hyperglycemia, hypertension, edema, bloating or gastric distress, aseptic necrosis of the hip, and hirsutism. Vascular changes such as polyarteritis nodosa or an increased tendency for thrombophlebitis have been reported. Ulcerative esophagitis and acute pancreatitis have occurred during, and may be related to, corticosteroid therapy. *Some corticosteroids such as the fluoro analogues of prednisolone appear to exert a relatively greater muscle wasting effect.* The incidence, type and severity of untoward reactions is usually related to the size of the dose and duration of therapy. For example, prolonged use of corticosteroids may also cause growth suppression (reversible on withdrawal) in children, delayed wound healing, or posterior subcapsular cataracts in adults. Because of the greatly enhanced anti-inflammatory activity of dexamethasone, lower doses can be used thus preventing or minimizing abnormal salt and water retention or potassium loss. Periodic serum potassium determinations are advised during prolonged therapy.

*It may be used as adjuvant therapy in certain infectious diseases providing such infections are adequately controlled by appropriate antibiotics or chemotherapeutic agents. It must be remembered that the anti-inflammatory effects of corticosteroids may mask signs of infection and such patients should be carefully observed. While average doses will usually not increase insulin requirements in controlled diabetics, when the drug is used in such patients, they should be observed closely for evidences of increased hyperglycemia or glycosuria. Periodic determinations of blood sugar during prolonged therapy are advised.*

*Post-injection flare-up of joint pain may sometimes be seen following intra-articular injection. Instability of a joint following repeated intra-articular injections is a rare occurrence.*

*It is safest to assume that prolonged therapy will result in depression of adrenocortical function. For this reason the drug should be withdrawn gradually when treatment is to be discontinued. It may be advisable to administer ACTH during this period to hasten the return of normal function. Should the patient be subjected to surgery, severe trauma, or shock within one year following withdrawal it may be advisable to give a temporary course of corticosteroid therapy. If this product is employed, supplementary salt and/or desoxycorticosterone should be used. Because of supplemental therapy required, dexamethasone is not the drug of choice in adrenal insufficiency.*

**Dosage**—The dose for intramuscular or intravenous administration varies from 4 to 20 mg, depending on the nature and severity of the disease being treated. *Intravenous doses exceeding 8 mg. (2cc) should be given slowly over a period of one minute. The initial dose may be repeated as necessary until the desired response is noted but the daily dose, with few exceptions, need not exceed 80 mg.*

Maintenance doses average 2 to 4 mg. daily. After achieving satisfactory control the patient should be switched to oral therapy as soon as feasible.

The dose for intrasynovial administration is usually 4 mg. for large joints and 0.8 to 1 mg. for small joints. For soft tissue and bursal injections a dose of 2 to 4 mg. is recommended. Ganglia require a dose of 1 to 2 mg. A dose of 0.4 to 1 mg is used for injection into tendon sheaths and helomata. Injections into inter-vertebral joints should not be attempted at any time and hip joint injection cannot be recommended as an office procedure.

Intrasynovial and soft tissue injections should be employed only when affected areas are limited to 1 or 2 sites. It should be remembered that corticoids provide palliation only and that other conventional or curative methods of therapy should be employed when indicated.

Supplied—5-cc (4 mg/cc) multiple dose vial; 1-cc (4 mg/cc) vial, box of 25.

LAKESIDE LABORATORIES,  
Milwaukee, Wis., November 1967.

DEAR DOCTOR: The Food and Drug Administration have requested that we call your attention to the monograph for Norpramin (desipramine hydrochloride) in the 1967 PDR: page 687, white section. The FDA consider this monograph incomplete (in relation to the official labeling, the package insert), and therefore potentially misleading as prescribing information to allow safe and effective use of the drug.

To provide you with the necessary adequate reference, we enclose a revised monograph for 1967 Physicians' Desk Reference in which the changes have been emphasized by italics. Please insert this revision opposite page 687.

Sincerely yours,

WILLIAM C. JANSSEN, M.D.

(Insert opposite p. 687—PDR, 1967 edition)

(NOTE.—Prescribing information for Norpramin which appears in the 1967 edition of PDR has been revised. The following is the new monograph and completely replaces the old one. Changes are emphasized by means of italics.)

#### NORPRAMIN

##### (Desipramine hydrochloride)

**Composition:** Norpramin (desipramine hydrochloride) (10, 11-dihydro-5-(3-methylaminopropyl)-5H-dibenzo [b, f] azepine hydrochloride), available in two dosage sizes: 25 mg. tablet, round, sugar coated, yellow; 50 mg. tablet, round, sugar coated, light green.

**Action and Indications:** Norpramin (desipramine hydrochloride) is a primary active metabolite of imipramine. It differs from earlier antidepressants in its rapid onset of action. Approximately 60 to 70% of patients with neurotic or psychotic depressions will respond satisfactorily. More than half will begin to improve in 2-5 days, others within a week. Usually, patients not responding within one week are less likely to improve. Norpramin is useful in the treatment of neurotic and psychotic depressive reactions, and in manic depressive or involutional psychotic reactions. It may be used as co-therapy with tranquilizers in the treatment of markedly agitated forms of depressions.

**Contraindications:** (1) Norpramin should not be given in conjunction with or within two weeks of treatment with a monoamine oxidase inhibitor. (2) Because of its physiologic effects (both anticholinergic and epinephrine potentiating), it is contraindicated in patients with glaucoma, urethral or ureteral spasm and recent myocardial infarction. (3) The presence of severe coronary heart disease with EKG abnormalities indicating a progressive disability and symptoms of heart failure due to this disability is likewise a contraindication. (4) Active epilepsy as it lowers the threshold for epileptiform seizures.

**Warnings (Relative Contraindications):** Palpitations, due to tachycardia, have been observed with desipramine hydrochloride therapy. Desipramine hydrochloride should be given therefore to patients with a history of paroxysmal tachycardia only with awareness that palpitations may be induced. In some such patients, the myocardium may not be in condition to tolerate well the increased work and decreased perfusion incident to such paroxysms.

*In two instances transient jaundice, probably analogous to that seen previously with chlorpromazine and (infrequently) with imipramine, has been noted; liver function studies in suspect cases, prior to and during prolonged desipramine hydrochloride therapy are thus advised.*

*In patients suspected of having glaucoma or urinary or gastric retention, the anticholinergic nature of the drug may be deleterious.*

*Patients receiving thyroid hormone, or sympathomimetic drugs may experience potentiation of the effects of these drugs, resulting in behavioral and/or cardiovascular toxicity. Patients receiving desipramine hydrochloride and anticholinergic drugs simultaneously are known to experience enhanced atropine-like side effects.*

*Animal teratology studies have proved negative. However, the drug is new and there is little clinical information about its use during pregnancy. Consideration of the possible risks relative to benefits should guide the decision to use Norpramin (desipramine hydrochloride) in women who are pregnant or who may be anticipated to become so.*

**Precautions:** (1) Norpramin treatment should not be substituted for hospitalization or restraint if the risk of homicide or suicide is considered grave. (2) In patients with manic depressive illness, Norpramin may induce a hypomanic state after the depressive phase terminates. (3) As with any drug, death may ensue from the suicidal ingestion of large doses of desipramine hydrochloride. (4) Discontinue therapy prior to elective surgery. (5) Use with caution in patients receiving sympathomimetic drugs or thyroid hormone as potentiation of the action of these drugs may occur. (6) Reduce dosage, or alter treatment, if serious adverse effects occur.

**Adverse Effects:** Undesired side effects in the desipramine hydrochloride treated patients were usually well tolerated; only occasionally did therapy have to be discontinued because of them. The side effects of desipramine hydrochloride were considered to be similar to those of imipramine; in general, these can be expected in about one of four patients.

The following side effects have been encountered: dry mouth, constipation, dizziness, palpitation, delayed urination, agitation and stimulation ("jumpiness", "nervousness", "anxiety", "insomnia"), bad taste, sensory illusion, tinnitus, sweating, drowsiness, headache, hypotension (orthostatic), flushing, nausea, cramps, weakness, blurred vision and mydriasis, rash, tremor, allergy (general), altered liver function, ataxia and extrapyramidal signs, agranulocytosis.

Additional side effects more recently reported include: seizures, eosinophilia, confusional states with hallucinations, purpura, photosensitivity, galactorrhea, gynecomastia, and impotence. Side effects which could occur (analogy to related drugs) include weight gain, heartburn, anorexia, and hand and arm parasthesias.

**Dosage and Administration:** Optimal results are obtained at about 150 mg./day. Dosage over 200-225 mg./day increases incidence of side effects. Norpramin may be administered as follows: two tablets (50 mg.) t.i.d. (150 mg./day). Partial response may be expected within 2-5 days; optimal response within 2-3 weeks. After optimal results are achieved a maintenance dose . . . 50-100 mg./day . . . should be sought.

An alternate method of giving Norpramin (desipramine hydrochloride) which may, however, delay the rapid onset of therapeutic response is: One tablet (25 mg.) three or four times a day= 75 or 100 mg. with a 25 mg. increment every few days, if needed, to a maximum dose of 200 mg. per day.

**Overdosage:** (1) Prevention: Keep out of reach of children. (2) Treatment: Gastric lavage, catharsis. For coma and circulatory collapse: adequate fluids, oxygen, assisted respiration, assisted cardiac impulse. Do not hesitate to digitalize. Use sympathomimetic drugs with caution. For seizures: parenteral barbiturates or diphenylhydantoin (note: diphenylhydantoin, though having an antiarrhythmic effect, has not been fully defined in respect of its effect on the heart or its rhythm.)

Blood dialysis is of little avail; continuous gastric lavage has been advocated on the basis of desipramine resecretion in gastric juice.

**Supplied:** Norpramin (desipramine hydrochloride) tablets of 25 mg., in bottles of 50, 500, and 1000; and tablets of 50 mg., in bottles of 30, 250, and 1000.

THE S. E. MASSENGILL CO.,  
Bristol, Tenn., November 1, 1967.

DEAR DOCTOR: The Food and Drug Administration has requested that we call your attention to the monographs for our products, Predsem, Saleort and Saleort-Delta, in the current (1967) *Physicians' Desk Reference*. The FDA considers these monographs to be incomplete in presenting the necessary information for the safe and effective use of these drugs and therefore potentially misleading.

To provide you with the necessary information, we enclose revised monographs for insertion at page 812 of your current (1967) PDR. The nature and extent of the additions and other revisions in the enclosed monographs are emphasized by use of italics.

Sincerely,

ROBERT P. EWING,  
Vice President, Marketing.

#### PROFESSIONAL PRODUCTS INFORMATION (P. 812)

##### PREDSEM

**Composition:** Each multiple-compressed white tablet contains:

Prednisone -----	5.0 mg.
Calcium pantothenate-----	10 mg.
Aluminum hydroxide gel, dried-----	0.2 Gm.
Magnesium trisilicate-----	0.1 Gm.

*Prescribing information for Predsem which appears on page 812 of the 1967 PHYSICIAN'S DESK REFERENCE has been revised and is completely replaced by the following. The nature and extent of the additions and other revisions in the monograph are emphasized by use of italics.*

**Action and uses:** For the treatment of the acute phase of rheumatoid arthritis and related diseases. Also of value in other conditions in which corticosteroid therapy is indicated. Antacids are incorporated to reduce gastric distress caused by hyperacidity in relation to steroid therapy.

**Contraindications:** Tuberculosis (active or latent), chronic nephritis, acute psychosis, Cushing's syndrome, peptic ulcer and in patients prone to thrombophlebitis. *Herpes simplex of the eye is usually an absolute contraindication. The appearance of ocular herpes simplex in patients receiving adrenocortical steroids systemically, or locally in the eye for other conditions, has been reported. If this occurs, Predsem Tablet should be discontinued unless the need for them is greater than the risk to the function of the eye.*

**Relative Contraindications:** As in the case of other powerful therapeutic agents, the physician must weigh the advantages of treatment with prednisone against the possible harmful effects. In congestive heart failure, hypertension, diabetes, frank osteoporosis associated with senility or with rheumatoid arthritis, renal insufficiency, history of peptic ulcer and mental disease. Predsem must be administered with caution.

In patients with diabetes mellitus being treated for a concurrent disease amenable to therapy with Predsem Tablets, the hyperglycemia may be aggravated; therefore, the diabetic status must be followed and regulated with great care. Usually it is possible to control the diabetes by increasing the insulin dosage.

While euphoria is the usual psychic reaction to large doses of prednisone, occasionally pronounced psychic derangements may appear. Early symptoms include insomnia, swings in mood and increased psychomotor activity.

**Precautions:** Corticosteroids should be used with caution in congestive heart failure, diabetes, renal insufficiency, history of peptic ulcer and mental disease. Predsem can mask infections by interfering with elevation of temperature, etc. If there is any question, drug should be temporarily discontinued until accurate diagnosis is made. May be reinstated as soon as adequate measures have been taken to treat the infection.

**Special Precautions:** Furthermore, because edema and weight gain from prednisone are extremely infrequent, the physician must be especially on his guard to detect less conspicuous side effects.

*Management of Patient During Stress:* Prednisone in large doses may produce adrenal atrophy. The physician should assume the continued therapy with prednisone, similar to therapy with cortisone and hydrocortisones, will result in some depression of adrenocortical function. It may be advisable to institute rest periods and to stimulate adrenocortical function by the use of ACTH. If, after long-term therapy, the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly. However, a potentially critical degree of adrenal insufficiency may still persist, and for at least six months hydrocortisone in increased dosage proportionately much larger than the previously used prednisone should be administered if the patient is subjected to shock or significant stress such as surgery or trauma. Also, if a patient is subject to unusual stress, during prednisone therapy it should be continued usually in markedly increased dosage at least for the duration of the stress and immediately following it.

*Supervision of Patient Following Prednisone Therapy:* Continued supervision of the patient after discontinuation of prednisone is essential because there may be a reappearance of severe manifestations of the disease for which the patient was treated.

*Clinical Effects:* In rheumatoid arthritis initial benefit from prednisone has usually been seen in a day or two, diminution in subjective distress occurring promptly. The appetite improves rapidly, energy reappears, and a feeling of well-being develops. Objective conditions, such as joint involvements and pain on motion, recede gradually. The extent of return to normal is limited by the degree of irreversible pathological changes present.

Elevated sedimentation rates are decreased usually with a drop to or near normal. Low hematocrit and hemoglobin values tend to increase when prednisone is administered.

Discontinuance of therapy usually results in a return of symptoms in a few days.

*Dosage and Administration:* The suggested suppressive dosage for severe rheumatoid arthritis is 30 mg. (six 5 mg. tablets) per day. In less severe cases, 20 mg. (four 5 mg. tablets) per day will generally suffice. The suppressive dosage should be continued until a good response is noted. This will usually be three or four days, but this dosage may, if necessary, be continued for as long as seven days. If no response is noted within seven days, consideration should be given to the question of whether or not the disease under treatment is true rheumatoid arthritis.

*Maintenance:* Gradual reduction in dosage every 5 to 6 days by steps of 5 mg. (5 to 20 mg. daily provides adequate maintenance therapy for many patients).

*How Supplied:* In bottles of 30, 100 and 1,000 multiple-compressed monogrammed white tablets.

#### SALCORT

*Composition:* Each pink tablet contains:

Cortisone acetate.....	2.5	mg.
Sodium salicylate.....	0.3	Gm.
Aluminum hydroxide gel, dried.....	0.12	Gm.
Calcium ascorbate.....	60	mg.
(equivalent to 50 mg. ascorbic acid)		
Calcium carbonate.....	60	mg.

*Prescribing information for Salcort which appears on page 812 of the 1967 PHYSICIANS' DESK REFERENCE has been revised and is completely replaced by the following. The nature and extent of the additions and other revisions in the monograph are emphasized by use of italics.*

*Action and Uses:* Salcort is indicated in common rheumatic disorders and as a means of adjusting corticosteroid dosages in treating chronic cases of rheumatic disease. The complementary corticosteroid-salicylate supplemented with vitamin C provides effective corticosteroid therapy for a wide range of common rheumatic disorders with minimum risk of undesirable side effects. Salcort is of particular value for patients not responding to salicylates alone and with those in whom a larger dose of corticosteroid is neither necessary nor advisable.

*Administration and Dosage:* Maintenance dosage may require from 6 to 8 tablets to as little as 3 or 4 tablets daily, depending on severity of symptoms. Acute stages may require a high dosage of 4 tablets four times daily for two or three days, or until the acute episode subsides.

**Contraindications:** Tuberculosis (active or latent), chronic nephritis, acute psychosis, Cushing's syndrome, peptic ulcer and in patients prone to thrombophlebitis.

**Relative Contraindications:** In congestive heart failure, hypertension, diabetes, frank, osteoporosis associated with senility or with rheumatoid arthritis, and mental disease other than acute psychosis, Salcort must be administered with caution.

**Precautions:** Corticosteroids should be used with caution in congestive heart failure, diabetes, renal insufficiency, history of peptic ulcer and mental disease. Salcort will mask infections by interfering with elevation of temperature, etc. If there is any question, drug should be temporarily discontinued until accurate diagnosis is made. May be reinstated as soon as adequate measures have been taken to treat the infection.

*Cortisone is a potent hormonal substance. Although the greater anti-rheumatic action of cortisone is not accompanied by an increased tendency to produce undesired hormonal effects, patients receiving it should be observed for the possible development of any signs of such excessive hormonal manifestation.*

Daily weighing of the patient and, as indicated, measurement of fluid intake and output should be alone to detect early evidence of fluid retention. Restriction of the daily sodium intake to 2 Gm. or less may prevent or correct fluid retention. If salt and water retention occur, sodium intake should be further restricted and the dosage of cortisone reduced or discontinued.

In the presence of hypopotassemia, as detected by blood potassium determinations, characteristic changes in the electrocardiogram, and muscular weakness, the dietary potassium intake should be supplemented with 2 to 4 Gm. of potassium chloride daily and the dosage of cortisone reduced or discontinued.

Hyperglycemia and glycosuria may occur in nondiabetic individuals receiving cortisone. In patients with diabetes mellitus, the insulin requirements are increased.

While euphoria is the usual psychic reaction to cortisone, occasionally pronounced psychic derangements may appear. Early symptoms include marked insomnia, swings in mood and increased psychomotor activity.

Since the use of cortisone tends to depress the normal pituitary-adrenocortical mechanism, the patient should be carefully supervised not only during but following therapy, and treatment should be discontinued gradually. The occurrence of any unexpected stress, such as surgery, severe infections, or accidental trauma, during or for at least a year following treatment, is an indication for vigorous adrenocortical supportive therapy with cortisone acetate, or whole adrenocortical extracts. Dosage and duration of such therapy is governed by the severity of the stress and the patient's clinical status.

**How Supplied:** In bottles of 100 pink monogrammed tablets.

**Literature Available:** On request.

#### SACORT-DELTA

**Composition:** Each multiple-compressed yellow tablet contains:

Prednisone	1.0	mg.
Potassium salicylate	0.3	Gm.
Calcium pantothenate	5.0	mg.
Calcium ascorbate (equivalent to 25 mg. absorbic acid)	30	mg.
Aluminum hydroxide gel, dried	0.12	Gm.
Calcium carbonate	60	mg.

*Prescribing information for Salcort-Delta which appears on page 812 of the 1967 PHYSICIANS' DESK REFERENCE has been revised and is completely replaced by the following. The nature and extent of the additions and other revisions in the monograph are emphasized by use of italics.*

**Action and Uses:** For the treatment of the subacute, severe phase of rheumatoid arthritis and related disease, Salcort-Delta provides a prednisone dosage which is relatively high but may be adjusted to "long-term" therapy. In the subacute phase, the prednisone-salicylate combination is more effective than either agent when used alone. Salcort-Delta includes antacids to guard against gastric distress related to corticosteroid therapy.

**Contraindications:** Because of their prednisone content, Tablets Salcort-Delta are contraindicated in tuberculosis (active or latent), chronic nephritis, acute psychosis, Cushing's syndrome, active peptic ulcer, and in patients prone to thrombophlebitis. Salcort-Delta will mask infections by interfering with the

elevation of temperature, etc. If there is any question, the drug should be temporarily discontinued until an accurate diagnosis is made. It may be reinstated as soon as adequate measures have been taken to treat the infection.

*Herpes simplex of the eye is usually an absolute contraindication. The appearance of ocular herpes simplex in patients receiving adrenocortical steroids systemically, or locally in the eye for other conditions, has been reported. If this occurs, Salcort-Delta Tablets should be discontinued unless the need for them is greater than the risk to the function of the eye.*

*Relative Contraindications:* As in the case of other powerful therapeutic agents, the physician must weigh the advantages of treatment with prednisone against the possible harmful effects. In congestive heart failure, hypertension, diabetes, frank osteoporosis associated with senility or with rheumatoid arthritis, renal insufficiency, history of peptic ulcer and mental disease, Salcort-Delta must be administered with caution.

*In a patient with diabetes mellitus being treated for a concurrent disease amenable to therapy with Salcort-Delta Tablets, the hyperglycemia may be aggravated; therefore, the diabetic status must be followed and regulated with great care. Usually it is possible to control the diabetes by increasing the insulin dosage.*

*While euphoria is the usual psychic reaction to large doses of prednisone, occasionally pronounced psychic derangements may appear. Early symptoms include insomnia, swings in mood and increased psychomotor activity.*

*Precautions:* Since edema and weight gain due to prednisone are infrequent, the physician must be especially watchful for the development of less conspicuous side effects. The use of prednisone tends to depress the normal pituitary-adrenocortical mechanism and the patient should be carefully supervised, not only during, but following therapy. The dosage should be reduced very gradually, but even then a potentially critical degree of adrenocortical insufficiency may persist asymptotically for some time. Therefore, if the patient is subjected to stress, such as surgery or trauma within at least six months after therapy has been terminated, steroid therapy should be reinstated. Furthermore, if a patient is subjected to unusual stress while receiving Salcort-Delta Tablets, steroid therapy should be continued for the duration of the stress and immediately following it. In both instances, proportionately much larger dosages of prednisone, cortisone, or hydrocortisone than that of the previously used Salcort-Delta should be used during the stress. As the prednisone, cortisone, or hydrocortisone is being discontinued, Salcort-Delta may be resumed in the former dosage.

*After discontinuation of Salcort-Delta Tablets, continued supervision of the patient is essential, because there may be sudden reappearance of the disease for which the patient was treated.*

*In administering Salcort-Delta Tablets the possibility of the occurrence of the side effects of salicylates should be borne in mind. Any form of salicylates should be administered with caution to patients with hypoprothrombinemia and bleeding or with asthma and other allergic conditions.*

*Administration and Dosage:* Can be started at 12 tablets daily in divided doses and dose diminished as symptoms subside.

*How Supplied:* In bottles of 100 multiple compressed, monogrammed yellow tablets.

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THE UPJOHN CO.  
Kalamazoo, Mich., November 15, 1967.

**DEAR DOCTOR:** The Food and Drug Administration has asked us to call your attention to certain promotional messages for Medrol Tablets which the FDA regards as misleading.

Some journal advertisements have recommended use of Medrol 16 mg. Tablets by an alternate day dose regimen. Although reports of this usage have appeared in the literature, the FDA points out that information currently available and submitted by us to them is not adequate to justify this regimen as advertised. Consequently, we are ceasing all reference to alternate day therapy in our promotion of the product.

The monograph for Medrol Tablets in the 1967 *Physicians' Desk Reference* is considered by the FDA to be inadequate in presenting information for the safe and effective use of the product. To provide you with the necessary information, we enclose a revised monograph for insertion at page 1143 of your current (1967) *PDR*.

Sincerely yours,

FENIMORE T. JOHNSON, M.D.

(NOTE.—Prescribing information for Medrol (methylprednisolone) Tablets which appears on pages 1143-1144 of your 1967 *PDR* has been revised and is completely replaced by the following.)

MEDROL TABLETS

(Methylprednisolone)

**Composition:** Each tablet contains methylprednisolone 16 mg., 4 mg. or 2 mg.

**Action and Uses:** Medrol is indicated in conditions known to be responsive to corticoid therapy, including: (1) collagen diseases, (2) allergic diseases, (3) certain dermatological conditions, (4) acute ocular inflammatory disease, (5) certain leukemias and lymphatic neoplastic diseases, (6) ulcerative colitis, nephrosis and as adjunctive therapy in pulmonary and meningeal tuberculosis.

**Administration and Dosage:** The average total daily doses recommended should be given in four equally divided dosages and should be individualized according to the severity, duration and patient's response. The average daily dosage of Medrol is approximately two-thirds (0.7) the required daily dosage of prednisolone. Initial suppressive dosages should be continued for 3 to 7 days during which time satisfactory clinical response is usually obtained. Should there be no satisfactory response within 7 days, re-evaluation of the case to confirm the original diagnosis is indicated.

Reduction of dosage to maintenance levels should be accomplished slowly in decrements of not more than 2 mg. at intervals of 7 days when the initial daily dosage is 15 mg. or more. (See table below)

Adjustment of the dose level is indicated from time to time in concert with fluctuations in the disease activity and patient response. Experience has indicated that long-term benefits are greater when steroid maintenance is accomplished at the lowest possible dose level. Dose levels for protracted use of methylprednisolone should be in the range of 1.5 to 2.0 mg. daily for children and adolescents, 4 to 5 mg. daily for young women, 3 to 4 mg. daily for postmenopausal women, and 5 to 7 mg. daily for men. **IMPORTANT**—In the management of patients with chronic disease such as rheumatoid arthritis, methylprednisolone should be regarded as a valuable adjunct to be used in conjunction with but not as replacement for standard therapeutic measures.

Diuresis and increased excretion of sodium have occurred following administration of Medrol to adrenalectomized animals, normal human subjects and patients with cardiac edema or cirrhosis of the liver with ascites. These findings have suggested the value of this agent as adjunct to therapy of these and other forms of edema. Medrol has been reported to potentiate the actions of mercenial and carbonic anhydrase inhibiting diuretic agents and to restore response to diuretics in patients with resistant cardiac edema.

The use of corticoids in tuberculosis, while usually contraindicated, may be life saving when given with adequate and effective dosage of antituberculosis agents to patients with fulminating pulmonary tuberculosis or meningeal tuberculosis. Rapid improvement with defervescence, weight gain and clearing of pulmonary lesions have been reported.

**Adverse Reactions:** Adverse reactions associated with use of corticosteroids, including Medrol (methylprednisolone), include electrolyte imbalance, osteoporosis which is reversible only with difficulty, spontaneous fractures, aseptic necrosis of the hip, activation and complication of peptic ulcer including perforation and hemorrhage, hyperglycemia, glycosuria, hypertension, nervousness, acne, hirsutism, rounded facies, cutaneous striae, amenorrhea, cervicothoracic hump, acute pancreatitis, necrotizing angiitis, thinning of scalp hair, petechiae and purpura, posterior subcapsular cataracts occasionally requiring extraction, myopathy, growth retardation in children, relative adrenocortical insufficiency (particularly in times of stress due to trauma, surgery or severe illness), protein catabolism with negative nitrogen balance, weakness, aggravation or masking of infection, increased intracranial or intraocular pressure, thromboembolism, ulcerative esophagitis, psychic disturbances, abnormal euphoria, insomnia, headache, vertigo, facial flushing, sweating, and abnormal fat deposits.

When adverse reactions occur, they are usually reversible and disappear when the hormone is discontinued.

**Precautions:** Medrol (methylprednisolone) should be given only with full knowledge of the characteristic activity of, and the varied responses to, adrenocortical hormones.

Diabetes mellitus, hypertension and congestive heart failure may be aggravated by the administration of corticoids. However, concomitant administration of Medrol with diuretics may be beneficial in patients with cardiac edema. Negative nitrogen balance may occur with protracted maintenance therapy. Measures to counteract persistent nitrogen loss include a high protein intake and the administration, when indicated, of a suitable anabolic agent. Likewise, ecchymotic manifestations have occasionally been reported. If such reactions are serious or distressing to the patient, reduction in dosage or discontinuance of methylprednisolone therapy may be indicated.

While current investigations indicate that muscle weakness in patients receiving corticoids may occur in the presence of normal or low potassium levels and may be due to a disturbance in muscle metabolism, data indicate that the incidence of this complication is low with Medrol. This effect should be kept in mind and periodic serum potassium determinations performed in patients on prolonged therapy. In some instances, steroid-induced myopathy has actually improved when patients have been transferred to a preoisteroid such as Medrol from fluorinated steroids containing the 9-alpha-fluoro configuration.

Because Medrol manifests little sodium retaining activity, the usual sign of cortisone or hydrocortisone overdosage (i.e., increase in body weight due to fluid retention) is not a reliable index of overdosage. Hence, recommended dose levels should not be exceeded, and all patients should be under close medical supervision. All precautions pertinent to the use of prednisolone apply.

While corticoids may be considered as effective therapy in polyarteritis nodosa, current data indicates that such therapy may have an undesirable effect and may cause lesions characteristic of the disease. Likewise, data indicates that the use of corticoids may in some instances induce acute pancreatitis. The development of posterior subcapsular cataracts has been associated with prolonged, high dosage corticoid therapy. To minimize this effect, doses should be kept as low as possible when administered for prolonged periods.

Retardation of linear growth has been noted in children receiving corticoids for 6 months or longer. With methylprednisolone this has been noted with doses of 5 mg. per square meter of body surface per day or greater. Retardation is usually proportional to dose and following cessation of therapy, the growth rate may be accelerated. The growth of children receiving prolonged therapy should be observed carefully. If growth has been retarded, the dose should be reduced sufficiently to permit recovery before epiphyseal closure.

Continued supervision of the patient after cessation of Medrol (methylprednisolone) therapy is essential, since there may be a sudden reappearance of severe manifestations of the disease for which the patient was treated.

**Warning:** Because of its inhibitory effect on fibroplasia, methylprednisolone may mask the signs of infection and enhance dissemination of the infecting organism. Hence, all patients receiving methylprednisolone should be watched for evidence of intercurrent infection. Should infection occur, it must be brought under control by use of appropriate antibacterial measures, or administration of methylprednisolone should be discontinued.

Since methylprednisolone suppresses endogenous adrenocortical activity, it is highly important that the patient receiving methylprednisolone be under careful observation not only during the course of treatment but for some time after treatment is terminated. Adequate adrenocortical supportive therapy with cortisone or hydrocortisone, and including ACTH, must be employed promptly if the patient is subjected to any unusual stress such as surgery, trauma, or severe infection.

**Tuberculosis:** Use of corticoid therapy as an adjunct in pulmonary or meningeal tuberculosis must be based on careful assessment of all factors. Such therapy should not be instituted unless the tubercle bacilli are shown to be sensitive to the antituberculosis agent. Use of adequate and effective antituberculosis therapy currently with corticoid therapy is mandatory. When the tuberculous condition is complicated by fungal infections, corticoid therapy is contraindicated. "Rebound" fever, joint pains and temporary deterioration of pulmonary lesions as indicated by x-ray may follow corticoid withdrawal. Hypersensitivity to the antituberculosis agent may be unmasked by withdrawal of corticoid.

**Hematological Disorders:** Therapy with methylprednisolone has been effective in producing remissions with certain types of leukemia, in producing symptomatic improvement of patients with other lymphomatous diseases and in thromboцитopenia and hemolytic anemia. As a general rule, the therapy with corticosteroids produces remissions more frequently in acute lymphatic leukemia

than in other types of leukemia and remission occurs more frequently in children than in adults.

The sodium retaining properties of cortisone and hydrocortisone prevented the use of these agents in large doses. However, since Mdtol (methylprednisolone) demonstrates a lesser propensity for salt retention, the administration of massive doses of this compound may be less likely to be associated with troublesome fluid retention. It has been found that large doses of corticoids may be effective in producing remissions in some patients with acute granulocytic, acute monocytic, and chronic lymphocytic leukemia. Such therapy has been particularly helpful in controlling thrombocytopenia and hemolytic anemia associated with chronic lymphatic leukemia and other chronic lymphomas.

**Dosage**—Dosage varies with the individual patient and the condition being treated and ranges from 1 to 2 tablets (16 mg. size) 1 to 3 times daily. In some cases, doses of the order of 300 mg. daily have been employed. Following symptomatic control of production of a remission, the daily dose should be reduced by decrement to maintenance level or discontinuation.

**LUPUS ERYTHEMATOSUS:** Large doses of corticoids may be necessary to control the manifestations of acute systemic lupus erythematosus. When a rapid onset of action is desired, Solu-Medrol (methylprednisolone sodium succinate) may be injected intravenously for the first two or three doses. When therapy is initiated orally, daily doses as high as 32 to 96 mg. (two 16 mg. tablets 1 to 3 times daily) may be necessary to control symptoms. After symptoms have been controlled, the daily dose should be reduced by decrements to a maintenance dose of 8 to 20 mg. daily.

**CONTRAINDICATIONS:** Medrol, like other corticoids, is usually contraindicated in patients with latent, questionably healed or active tuberculosis. However, Medrol administered with antituberculosis agents may be life saving in certain cases. Absolute contraindications to corticoid therapy include herpes simplex keratitis and acute psychoses. Relative contraindications include: peptic ulcer.

**HOW SUPPLIED:** White, scored 16 mg. tablets in bottles of 50. White, scored 4 mg. tablets in bottles of 30, 100 and 500. Pink cross-scored 2 mg. tablets in bottles of 30 and 100. Medrol Dosepak—21 four mg. tablets with patient instructions for 6 days of countdown therapy.

(Shown in Product Identification Section.)

#### MEDROL® (METHYLSPREDNISOLONE): ADMINISTRATION AND DOSAGE TABLE

Disease	Initial daily dose	Daily maintenance dose
Rheumatoid arthritis:		
Severe.....	12 to 16 mg.....	6 to 12 mg.....
Moderate.....	6 to 8 mg.....	2 to 6 mg.....
Children.....	6 to 10 mg.....	2 to 8 mg.....
Lupus erythematosus.....	20 to 96 mg.....	8 to 20 mg.....
Allergic diseases.....	12 to 40 mg.....	4 to 16 mg.....
Ocular inflammatory diseases.....	12 to 40 mg.....	2 to 12 mg.....
Adrenogenital syndrome.....	16 to 60 mg.....	4 to 12 mg.....
Ulcerative colitis.....	20 to 60 mg. (for 10 to 14 days until diuresis occurs).	12 to 40 mg. (3 consecutive days of each week for 6 to 12 months).
Nephrosis.....	16 to 24 mg. (concurrently with other accepted therapy).	4 to 12 mg.
Refractory congestive heart failure .....	16 mg. for 10 to 12 weeks..... or 48 mg. for 14 days.....	Reduce by decrements in a period of 2 to 7 weeks. Reduce by decrements over 2-week period.
Tuberculosis: Pulmonary and meningeal (concurrently with antituberculous agents).		

ARMOUR PHARMACEUTICAL CO.,  
Chicago, Ill., November 16, 1967.

**DEAR DOCTOR:** The Food and Drug Administration has requested that we call your attention to the monograph for H.P.\*ACTHAR® GEL in the current (1967) *Physician's Desk Reference*. The FDA considers this monograph to be incomplete in presenting necessary information for the safe and effective use of this drug and, therefore, potentially misleading.

To provide you with the necessary information, we enclose a revised monograph for insertion at page 527 in your 1967 *PDR*. The nature and extent of the additions of previously omitted information are indicated by the use of italics.

Sincerely yours,

J. A. HUBATA, M.D.,  
Medical Director.

(NOTE.—Prescribing information for H.P.\* ACTHAR® GEL which appears on Pages 527 and 528 of the 1967 *PDR* has been revised and is completely replaced by the following. The nature and extent of the additions of previously omitted information are indicated by the use of italics.)

ARMOUR PHARMACEUTICAL COMPANY

CHICAGO, ILL.

H. P.\* ACTHAR® GEL

(Repository Corticotropin injection)

Highly Purified

AND

ACTHAR®

(Corticotropin injection)

**Description:** H.P.\* ACTHAR GEL (Repository Corticotropin Injection) is a Highly Purified preparation of CORTICOTROPIN in gelatin which has both rapid onset and prolonged action. One injection may have 24- to 72-hour effectiveness. The high degree of purity also allows its administration by intravenous infusion. Each milliliter contains the labeled activity of Corticotropin U.S.P., 16% Gelatin, 0.5% Phenol, not more than 0.1% Cysteine (added) and Water for Injection, q.s. ACTHAR (Corticotropin Injection) is sterile powdered lyophilized ACTH which in the dry form is stable at room temperature. Each vial contains the labeled activity of Corticotropin U.S.P. and approximately 9 milligrams of hydrolyzed Gelatin.

**Actions:** ACTHAR (Corticotropin Injection) is the Armour Pharmaceutical Company brand of ACTH (Corticotropin). ACTH is the anterior pituitary hormone which stimulates the functioning adrenal cortex to produce and secrete all of its steroids, which number over 30. In contrast, corticosteroids may depress adrenal cortical function and produce adrenal atrophy. The fact that ACTH acts directly on the adrenal cortex provides a rationale for use of ACTH in treatment of the adrenal insufficiency produced by cortisone, hydrocortisone, prednisone and prednisolone.

**Indications:** *Allergic Diseases*—Angioneurotic Edema, Asthma, Drug Reactions, Hay Fever, Serum Sickness. **Note:** Epinephrine is the drug of choice for acute allergic reactions, corticotropin or steroid therapy being adjunctive. *Collagen Diseases*—Acute Rheumatic Fever; Arthritis, Rheumatoid; Bursitis; Lupus Erythematosus; Periarteritis Nodosus; Psoriatic Arthritis; Scleroderma; Spondylitis, Rheumatoid; Still's Disease; Tenosynovitis. *Dermatologic Diseases*—Anogenital Pruritus, Atopic Dermatitis, Dermatitis Venenata, Dermatitis Medicamentosa, Exfoliative Dermatitis, Dermatomyositis, Pemphigus, Psoriasis, Urticaria. *Endocrine Diseases*—Panhypopituitarism. *Eye Diseases*—Choroiditis; Conjunctivitis; Glaucoma, Acute Secondary; Iritis; Keratitis; Optic Neuritis; Sympathetic Ophthalmia; Uveitis. *Hemolytic Diseases*—Acquired Hemolytic Jaundice. *Other Uses*—ACTHAR (Corticotropin) preparations have also been used in numerous other disease states such as: Agranulocytosis; Aplastic Anemia; Bell's Palsy; Beryllium Poisoning; Burns; Erythema Nodosum; Erythroblastosis Fetalis; Fibrosis; Gout; Guillain-Barre Syndrome; Heat Sickness; Hepatic Coma; Hodgkin's Disease; Hypoglycemia, Idiopathic; Infections, Acute Overwhelming (e.g., Peritonitis, Meningitis); Insect Bites; Leukemias, Acute and Chronic; Lymphatic; Loeffler's Syndrome; Myositis; Nephrotic Syndrome; Neuritis; Orchitis; Rhinitis; Sarcoidosis; Shoulder-Hand Syndrome; Snake Bite; Sprue Syndrome; Stevens-Johnson Syndrome; Thyroiditis; Ulcerative Colitis.

*Contraindications:* "Absolute Contraindications": Tuberculosis (active, healed or questionably healed), ocular herpes simplex, and acute psychosis are usually absolute contraindications to corticotropin therapy. Corticotropin is of no value in patients with Addison's Disease or after adrenalectomy since its action depends on the integrity of the adrenal cortex.

"Relative Contraindications": (1) Relative contraindications are Cushing's Disease, congestive heart failure, diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, thromboembolic tendencies, osteoporosis, diabetes mellitus, psychotic tendencies and acute or chronic infections (especially varicella or vaccinia) as well as other exanthematos and fungal diseases. (2) Pregnancy is a relative contraindication to corticotropin therapy, particularly during the first trimester, because fetal abnormalities have been observed in experimental animals. (3) If corticotropin is used in the above conditions, the risks should be weighed against the possible benefits.

*Warning:* Skin testing should be considered prior to treatment of patients with known or suspected sensitivities to corticotropin (which is a polypeptide) or porcine proteins. It is recommended that all patients be observed for a period of at least 15 minutes following administration of corticotropin. Epinephrine 1:1000 for emergency treatment should be available.

*Precautions:* (1) Corticotropin should be given only with full knowledge of the characteristic activity of, and the varied responses to, this preparation. (2) Average and large doses of corticotropin can cause elevation of blood pressure, salt and water retention, and increased potassium and calcium excretion. *The hypertension may be transitory during a period of electrolyte and water retention. Observe blood pressure responses until the maintenance dose is established.* Dietary salt restriction and potassium supplementation may be necessary. *If this does not control fluid retention, decrease the dose, omit a few injections until diuresis occurs, administer a diuretic, or consider discontinuation of therapy. Daily weights should be charted as a guide to abnormal weight gains.* Muscle weakness, fatigue or paresthesias may be a reflection of potassium deficiency, but are seldom observed if a potassium supplement is added to the diet. *EKG's or serum potassium levels are recommended guides if ACTH or corticoids are administered at high dosage levels for prolonged periods. If necessary, decrease the dosage or temporarily interrupt treatment and resume at a later date on a high potassium regimen.* (3) *Corticotropin may mask the signs of infection and enhance dissemination of the infecting organism. Hence all patients receiving corticotropin should be watched for evidence of intercurrent infection.* Chest x-rays should be done at regular intervals during prolonged therapy. *Should infection occur, initiate vigorous, appropriate anti-infective therapy. Abrupt cessation of corticotropin should be avoided if possible because of the danger of superimposing adrenocortical insufficiency on the infectious process.* (4) Since spontaneous remission of some diseases, such as rheumatoid arthritis, may occur during pregnancy, every effort should be made to avoid hormone treatment in pregnancy. (5) To avoid relative pituitary hypofunction, corticotropin therapy should be terminated gradually, particularly when patients are receiving large doses or have undergone prolonged treatment. Furthermore, if such patients are subjected to undue stress, such as surgery or trauma, while being treated or within one year after treatment has been terminated, hormone therapy should be augmented or reinstated and continued for the duration of the stress period and immediately following it. It is preferable to use corticotropin and/or cortisone or hydrocortisone in the immediate preoperative and postoperative periods. (6) Continued supervision of the patient after cessation of corticotropin is essential, since there may be a sudden reappearance of severe manifestations of the disease for which the patient was treated. (7) *Long-term corticotropin therapy may be accompanied by gastric hyperacidity and/or peptic ulcer. It is recommended, therefore, that patients with a history of peptic ulcer be placed on an ulcer regimen (including administration of an antacid) as a prophylactic measure.* Peptic ulcer patients complaining of gastric distress should be the subjects of appropriate x-ray examinations of the gastrointestinal tract. (8) Corticotropin may aggravate diabetes mellitus so that higher insulin dosage may become necessary or manifestations of latent diabetes mellitus may be precipitated. *Frequent urine sugar determinations and two hour postprandial blood sugar determinations are recommended during the period of dosage adjustment.* (9) Psychotic changes may be observed. *If exaggerated euphoria, nervousness, pronounced insomnia or depression occur, reduce or discontinue therapy and administer sedatives as indicated.*

*Adverse Reactions:* Adverse reactions, when they occur, are usually reversible and disappear when corticotropin is discontinued. Abscess, sterile. Activation and complication of peptic ulcer (including perforation and hemorrhage). Aggravation or masking of infection. Alteration of Glucose Metabolism, with aggravation of diabetes mellitus, including hyperglycemia and glycosuria. Aseptic Necrosis of Hip and Humerus. Convulsions. Cushing's Syndrome (including moon facies, suprascapular fat pads, hirsutism, striae, and acne). Electrolyte imbalance. Facial Erythema. Headache. Increased Blood Pressure. Increased Intra-cranial Pressure with Papilledema (pseudo-tumor cerebri). Increased Intraocular Tension. Insomnia. Menstrual Irregularities. Myopathy. Necrotizing Angitis. Osteoporosis (reversible only with difficulty). Pancreatitis. Petechiae and Purpura. Posterior Subcapsular Cataracts (occasionally requiring extraction). Postinjection Flare. Protein Catabolism (with negative nitrogen balance). Psychic Disturbances (especially abnormal euphoria). Spontaneous Fractures. Suppression of Growth in Children. Sweating. Thromboembolism. Ulcerative Esophagitis. Vertigo. Weakness.

*Dosage and Administration: Directions for Use of ACTHAR (Corticotropin)*

*Preparations*—Clinical response is the criterion of adequate dosage. Unusual laboratory studies are not necessary. Because the adrenals vary in their sensitivity to stimulation by ACTH there can be no specific, uniform dose effective for all individuals. The aim is to obtain a therapeutic effect with minimal dosage and with minimal or no metabolic alterations. A clinical response is secured within 2 weeks in the majority of conditions. Once the disease is under control, decrease the total daily dose as rapidly as possible consistent with maintaining a remission—thus try to reduce the total dose to about 75% of that needed initially. If adequate, this dosage is continued for 3-7 days before making a further similar reduction. When the lowest daily maintenance dose is thus established, attempts should be made at lengthening the interval between doses. If symptoms are not suppressed after dosage reduction, return to the previous effective schedule. If the nature of the disease requires maintenance therapy, aim to employ the smallest effective dose with the longest possible interval between injections. If the doses needed for full relief produce significant "side effects", reduce the dose and be satisfied with less than full suppression of disease under management.

*Administration and Dosages of H.P. ACTHAR GEL (Repository Corticotropin Injection) and ACTHAR (Corticotropin Injection):* Either H.P. ACTHAR GEL (Repository Corticotropin Injection) or ACTHAR (Corticotropin Injection) may be given subcutaneously, intramuscularly, or as an intravenous infusion. Since ACTHAR (Corticotropin Injection) is a lyophilized preparation, it must be reconstituted before administration by dissolving in a convenient amount of Water for Injection or Sodium Chloride Injection in such a manner that an individual dose will be contained in 1-2 cc. of solution. Like all aqueous solutions of ACTH, ACTHAR (Corticotropin Injection) is usually given every 8-12 hours. When reconstituted, the solution should be refrigerated. *SUBCUTANEOUS OR INTRAMUSCULAR TREATMENT OF SPECIFIC DISEASES*—Note: The dosages expressed are for H.P. ACTHAR GEL (Repository Corticotropin Injection) only. For ACTHAR (Corticotropin Injection) give the same total daily dose stated for H.P. ACTHAR GEL (Repository Corticotropin Injection) but give this in 3 divided doses every 8 hours initially. Tapering and maintenance regimens should be carefully observed.

For children under 40 lbs. in weight, reduce by one-third the dose recommended below. The dosages stated below for specific diseases are suggestive only and not absolute.

*ADRENAL INSUFFICIENCY*—secondary to pituitary deficiency or to corticoid-induced adrenal atrophy. As a rule, 100 Units daily for 3 days will reactivate the corticoid-suppressed adrenal and 40 Units twice a week or 100 Units weekly will prevent adrenal atrophy induced by the administration of corticosteroids.

*ALCOHOLISM* and *D.T.'S*—40-60 Units once daily; recovery usually within 36 hours. Injections may be continued 3 times a week for several weeks.

*ANGIONEUROTIC EDEMA*—60-80 Units once daily or 40-50 Units b.i.d. if severe; maintenance treatment not required if cause removed.

*ANOGENITAL PRURITIS*—60-80 Units once daily or 40-50 Units b.i.d. if severe.

*ARTHRITIS, RHEUMATOID* including *SPONDYLITIS, STILL'S DISEASE* and *PSORIATIC*—60-80 Units once daily; 40-50 Units b.i.d. for severe cases. Maintenance therapy usually required.

*ASTHMA*—60-80 Units daily or 40-50 Units b.i.d.; maintenance treatment may be necessary.

*BURNS*—60-80 Units daily or 40-50 Units b.i.d. if severe; give for 5-10 days reducing dosage as patient's condition improves.

*BURSITIS*—60-80 Units daily; results in hours especially in acute cases.

*COLITIS, Ulcerative*—60-80 Units daily or 40-50 Units b.i.d. for severe

*cases: continue until mucosa appears relatively normal. The most dramatic results are seen in the acute cases.* DERMATITIS, CONTACT, DRUG, ETC.—60–80 Units daily or 40–50 b.i.d. if severe; maintenance treatment not required if cause removed. DERMATOMYOSITIS—60–80 Units daily; 40–50 Units b.i.d. if severe; maintenance treatment usually required. EXFOLIATIVE DERMATITIS—60–80 Units daily or 40–50 Units b.i.d. if severe; continue for 2 weeks after skin is essentially normal; maintenance usually not required if cause determined. EYE DISEASES: CHOROIDITIS, CONJUNCTIVITIS; ACUTE SECONDARY GLAUCOMA, IRRITIS, KERATITIS, SYMPATHETIC OPHTHALMIA, OPTIC NEURITIS—60–80 Units once daily or 40–50 Units b.i.d. for severe cases; continue treatment until lesion healed. GOUT—60–80 Units once daily or 40–50 Units b.i.d. if severe; result usually in 1–3 injections. Concurrent colchicine therapy advised. GUILLAIN-BARRE SYNDROME—60–80 Units daily or 40–50 Units b.i.d. if severe. HAY FEVER—60–80 Units once daily or 40–50 Units b.i.d. if severe; periodic injections advisable during pollen season. HYPOGLYCEMIA, Congenital Idiopathic—40–60 Units daily; small amounts may be required to maintain control. JAUNDICE, Hemolytic Acquired—40–60 Units daily until blood picture normal; maintenance treatment unless cause removed. LUPUS ERYTHEMATOSUS—40–80 Units b.i.d. and continue for several weeks after adequate remission; maintenance treatment usually required. NEPHROTIC SYNDROME—For patients weighing 50–100 lbs., 60 Units once daily; 100 lbs. or over, 80 Units daily. Initial dose is continued 10–12 days and then abruptly stopped to allow for spontaneous diuresis; diuresis may occur before 10 days. If edema disturbing, stop treatment diuresis may occur. If diuresis inadequate, repeat after 5 days. Patients are kept on usual nephrotic regimens during therapy. PANHYPOPLUITARISM—20–40 Units daily; maintenance therapy indicated with smaller doses and lengthened intervals between doses. PEMPHIGUS—60–80 Units daily or 40–60 Units b.i.d. if necessary. Continue treatment for 10–14 days after old lesions heal and new lesions cease to appear. Most cases require maintenance therapy. PENICILLIN REACTIONS—See Dermatitis (Contact and Drug). PERIARTERITIS NODOSA—60–80 Units daily or 40–50 Units b.i.d. if necessary; maintenance treatment usually necessary. POISON IVY—See Dermatitis (Contact and Drug). PSORIASIS—60–80 Units daily or 40–50 Units b.i.d. until skin lesions essentially gone; maintenance therapy generally required. RADIATION SICKNESS—20–60 Units daily; symptoms usually controlled within few days. RHEUMATIC FEVER—60–80 Units daily or 40–50 Units b.i.d. if acutely ill. Continue for 2–3 weeks before tapering dose. Do not discontinue until clinical and laboratory signs of disease disappear, usually a total period of 6–8 weeks. Cardiac decompensation is not a contraindication—diuretics may be used. SARCOIDOSIS—40–80 Units daily; improvement usually within 5–7 days; maintenance therapy may be necessary. SERUM SICKNESS—40–80 Units once daily; if severe, 40–50 Units b.i.d. TENOSYNOVITIS—40–80 Units daily or 40–50 Units b.i.d. if severe; results usually within 24–36 hours. THYROIDITIS—80 Units daily for 3 days followed by 60 Units for 2 days, 40 Units for 2 days, 20 Units for 2 days, and 10 Units for 3 days. URTICARIA—60–80 Units daily or 40–50 Units b.i.d. if severe; maintenance therapy not required in cases with known etiology. ACTHAR (Corticotropin) preparations have also been used in a number of other diseases; Agranulocytosis (especially drug-induced), Aplastic Anemia, Bell's Palsy, Beryllium Poisoning, Erythema Nodosum, Erthroblastosis Fetalis, Fibrositis, Hepatic Coma, Heat Sickness, Hodgkin's Disease, Infections (acute overwhelming as Peritonitis, Meningitis, etc.), Insect Bites, Leukemia (acute and chronic lymphatic), Loeffler's Syndrome, Myositis, Neuritis, Orchitis, Rhinitis, Scleroderma, Shoulder-Hand Syndrome, Snake Bite, Sprue Syndrome, Stevens-Johnson Syndrome.

**INTRAVENOUS USE:** This method of administration may be used where a rapid response is desired, in patients refractory to intramuscular ACTH, for reactivation of adrenals suppressed by cortisone, hydrocortisone, prednisone, prednisolone, etc., and for diagnosis. The recommended dose is 10–25 Units of ACTHAR (Corticotropin Injection) or 40 to 80 Units of H.P. ACTHAR GEL (Repository Corticotropin Injection) in 500 cc. of 5% glucose in water given as a continuous intravenous infusion over an eight hour period, once daily. For children under 6 years, reduce the dosage to 50% of the adult dose recommended for the ACTHAR (Corticotropin Injection) preparation being used. There is no long-acting effect when H.P. ACTHAR GEL (Repository Corticotropin Injection) is used intravenously. Patients known to be highly sensitive to proteins should be carefully evaluated even though the slowness of infusion and the normal blocking effect of ACTH in hypersensitivities would appear to offset reactions. Patients

should be watched closely for the first 30 minutes; epinephrine should be available. Tapering can be started much sooner than when ACTH is given intramuscular or subcutaneously because with continuous intravenous infusion, clinical results are obtained more rapidly. After obtaining a remission by the intravenous route, further therapy, if necessary, is usually given subcutaneously or intramuscularly in the form of H.P. ACTHAR GEL (Repository Corticotropin Injection) which because of its repository properties fewer injections are required.

**LABORATORY TESTS OF ADRENAL CORTICAL FUNCTION:** (1) *The Four Hour or Thorn Test*—An eosinophil count is made in the fasting state and immediately thereafter 25 Units of ACTHAR (Corticotropin Injection) are injected intramuscularly. Another eosinophil count is made 4 hours later. Breakfast may be given following the first eosinophil count but lunch should be withheld until after the second. A fall in eosinophils of 50% or more below the pre-injection level indicates a satisfactory adrenal cortical response. (2) *The 8 Hour I.V. Test*—25 Units of ACTHAR (Corticotropin Injection) in 500 cc. of 5% dextrose are infused over an 8 hour period. Eosinophils are counted at 0 and 8 hours; a fall of 50% or more is indicative of a responsive adrenal.

**PACKAGE FORMS:** H.P. ACTHAR GEL (Repository Corticotropin Injection) is supplied in 5 milliliter multiple-dose vials in strengths of 40 and 80 U.S.P. Units (I.U.) per milliliter; 1 milliliter vials containing 40 and 80 U.S.P. Units (I.U.) per milliliter; and 1 milliliter B-D disposable syringes containing 40 U.S.P. Units (I.U.) per milliliter. ACTHAR (Corticotropin Injection) is supplied as a lyophilized powder in vials containing 25 and 40 U.S.P. Units (I.U.) per vial.

**PHYSICIANS' DESK REFERENCE,  
Oradell, N.J.**

DEAR SIR: The Food and Drug Administration has requested that we call your attention to the monographs for the following products in the current (1967) Physicians' Desk Reference :

	Page
HP Acthar Gel-----	527
Cortrophin Gel-----	898
Cortrophin-Zinc -----	898
Hexadrol -----	899
Hexadrol Phosphate Injection-----	899
Norpramin -----	687
Predsem -----	812
Saleort -----	812
Saleort-Delta -----	812

The FDA considers these monographs to be incomplete in presenting the necessary information for the safe and effective use of these drugs and therefore potentially misleading.

To provide you with the necessary information, we enclose revised monographs for insertion in your 1967 PDR at the pages indicated at the top of each sheet.<sup>1</sup> The nature and extent of the additions and other revisions in the enclosed monographs are emphasized by the use of italics.

Sincerely,

ALBERT B. MILLER,  
*General Manager.*

PARKE, DAVIS & Co.,  
*Detroit, Mich., January 15, 1968.*

DEAR DOCTOR: The Food and Drug Administration has asked us to call your attention to our recent Ponstel® (mefenamic acid) journal advertisement and certain promotional mailing and detailing pieces which the Food and Drug Administration regards as misleading.

The introductory campaign featured results from non-blind clinical trials using only a single 500 mg. dose for several types of pain. The Food and Drug Administration points out that Ponstel has also been studied in several double-blind clinical trials in which the drug was compared to aspirin and other non-narcotic analgesics. These trials demonstrated that Ponstel was essentially equal

<sup>1</sup> Retained in committee files.

to the comparison drug and better than placebo. However, in certain individual trials aspirin was found better than Ponstel and the latter could not be distinguished from placebo; in some trials pain relief with placebo was obtained in as high as 40% of the patients. In other trials the results with Ponstel were better than those with aspirin or placebo.

The Food and Drug Administration considers that the introductory campaign failed to give adequate prominence to the fact that Ponstel is indicated for short-term administration not exceeding one week of therapy. Also, in a promotional brochure, results were reported from a double-blind effectiveness comparison with codeine and placebo, which represented that Ponstel was equal in effectiveness to 25 mg. of codeine. However, the dosage of Ponstel employed in this study was at a level which is still in the investigational phase.

We are discontinuing the advertising campaign in question.

Sincerely,

J. E. GAJEWSKI, M.D.

SYNTEX,

January 22, 1968.

DEAR DOCTOR: The Food and Drug Administration has asked us to call your attention to the fact that certain statements in recent advertising for our oral contraceptives, Norquen® and Norinyl®-1, may be misleading.

In the Norquen advertisement, the paragraph headed "Low incidence of side effects" emphasizes the low incidence of certain less serious side effects such as spotting, break-through bleeding, nausea, vomiting and other gastrointestinal disturbances, but fails to give adequate emphasis to the more serious known side effects such as cholestatic jaundice, rise in blood pressure in susceptible individuals, and mental depression which also occur in low incidence. Further, although a cause and effect relationship has neither been established nor disproved, the advertisement does not give adequate emphasis to the possible occurrence of thrombophlebitis, pulmonary embolism, and neuro-ocular lesions which have been observed in users of oral contraceptives.

The advertisements for both Norquen and Norinyl-1 state that "careful observation and caution are required for patients with symptoms or history of . . . cerebrovascular accident, psychic depression. . . ." The ads should have been more specific in stating:

"Oral contraceptives should be used with caution in patients with a history of cerebrovascular accident and should be discontinued if there is a sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia, or migraine, or if examination reveals papilledema or retinal vascular lesions, since these may be symptoms of cerebrovascular accident."

The advertisements disclose that careful observation and caution are required for patients with symptoms or history of psychic depression but do not specifically state that oral contraceptives should be discontinued if psychic depression recurs to a serious degree. Also, the ads fail to disclose that a decrease in glucose tolerance has been observed in a small percentage of patients on oral contraceptives.

We are modifying all future advertising to reflect these changes.

Sincerely,

BEN Z. TABER, M.D.,  
*Medical Director.*

G. D. SEARLE & Co.,  
Chicago, Ill., January 26, 1968.

DEAR DOCTOR: In June 1967, the Food and Drug Administration and all manufacturers of oral contraceptives agreed on certain changes in the uniform portions of the labeling for all oral contraceptive products. These changes were to be included in all advertisements after October 1, 1967.

The FDA has asked us to call your attention to recent journal advertisements for Ovulen®-21, which departed from the new uniform labeling in several respects.

The original uniform labeling stated,

"The following occurrences have been observed in users of oral contraceptives. A cause and effect relationship has not been established:

"Thrombophlebitis

Pulmonary embolism

Neuro-ocular lesions."

Because that labeling did not accurately represent the present status of opinion concerning the possible danger of side effects, the warning statement was changed to read: "A cause and effect relationship has been *neither established nor disproved.*" [Italic supplied.] The FDA regards the advertisements as potentially misleading because they omitted this important change which emphasizes the possibility of these serious hazards.

Further, the advertisements failed to include the following side effects which, although causation has not been established, have been reported in users of oral contraceptives: an ovulation post treatment, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, backache, nervousness, dizziness, fatigue, headache, hirsutism.

We have modified our current advertising to reflect these changes.

Sincerely,

HERBERT HELLING,  
Food and Drug Administration Affairs.

ARDSLEY, N.Y., February 15, 1968.

DEAR DOCTOR: In our promotion of Persantine® (brand of dipyridamole) for long-term therapy in anginal patients, we sent a letter to physicians stating that "Several studies document the effectiveness of Persantine in extending walking distance and general increasing exercise tolerance." Enclosed with the letter was a reprint of a study in the *Journal of Chronic Diseases* of March 1967 to support the claims for effectiveness.

The Food and Drug Administration has asked us to inform you that the claims for effectiveness of Persantine, and many other drugs marketed prior to 1962, have been neither approved nor disapproved by the Agency. The FDA is proceeding on the basis that the Drug Amendments of 1962 require the Agency to evaluate the effectiveness of such drugs, and this is currently being done with the assistance of the drug efficacy panels of the National Academy of Sciences/National Research Council.

The FDA regards the promotional letter as potentially misleading because it presented only favorable information regarding the drug's effectiveness when there is a substantial body of opinion that does not support the claimed effectiveness of the product. For example, the AMA Council on Drugs (in *New Drugs* 1967) has stated that double-blind studies comparing dipyridamole with a placebo have shown equivocal results and that the drug has not been convincingly shown to be effective in the long-term treatment of angina pectoris.

Recently, in the *JAMA* issue of September 11, 1967, a paper by Sbar and Schrant disclosed results of a six-month double-blind study. The authors concluded that "The study failed to detect a statistically significant difference between the improvement in patients receiving dipyridamole and the improvement in patients receiving a placebo."

Our future promotion will express the range of expert medical opinion on the effectiveness of Persantine when any segment of that opinion is referenced.

GEIGY PHARMACEUTICALS.

Dr. McCLEERY. Also along the way of developing public awareness of the type of expectations which the FDA considered the law to require, the Commissioner of Food and Drugs had appeared before the Fountain Subcommittee of the House Committee on Government Operations, and had reviewed for them our programs in this important area of our public responsibilities.

In short, and in many ways, we felt that the industry's attention had been brought emphatically to promotion excesses in specific and in many ways.

As far as our experience with the problem represented by the drug under discussion today is concerned, we felt that there were three approaches to the promotion of this new product by Merck & Co., all of which had elements with which we disagreed—one of which was mentioned yesterday by Dr. Jennings, in his testimony, in the use of a "Dear Doctor" letter sent by the company, accompanying with it the

revision of the package insert, which was the occasion for the letter. We took exception to the promotional style of that letter, and that represented one episode in the history of this drug.

There was a second episode which I would like to speak about next, which was in regard to an article in the Pageant magazine—and a third, which I want to cover last, the advertising campaign used by Merck & Co. in reference to the subject drug for the medical profession in journals that go only to doctors.

Now, in June 1966, the director of public relations for Merck & Co., Mr. John Fletcher, wrote to Theodore O. Cron, our Assistant Commissioner for Education, enclosing a print of an article that was about to appear in the July 1966 issue of Pageant magazine.

**Senator NELSON.** Do you have a copy of that Pageant magazine article?

**Dr. McCLEERY.** Yes, sir, we will submit one for the record.

**Senator NELSON.** Would you submit that for the record?

**Dr. McCLEERY.** Yes, sir.

(The article referred to, for inclusion in the record, follows:)

[From Pageant Magazine, July 1966]

#### INDOCIN

A special report on a remarkable new drng that relieves the pain of arthritis, bursitis, gout, trick knee, tennis elbow, and sprains

(By Phyllis and Robert P. Goldman)

Two months ago a Miami housewife, aged 29, hobbled off the tennis court with a sharp, knife-like pain in her knee. She went home and lay down. But within five hours the knee was tender, inflamed, and stiff.

The housewife, Mrs. R. L., called her doctor, who, after examining the knee, declared, "Let's try something new, something that many of my patients are beginning to call a miracle drug."

Mrs. R. L. took the drug, and the most incredible thing happened. Within 36 hours she was no longer limping in pain. The knee swelling and stiffness began to subside. She found that she could walk almost normally. In a week the pain and inflammation had become simply a memory.

A Cleveland grandmother, Mrs. C. M., suffered for ten years from excruciating arthritis of the hip. Almost every available drug was tried, but not one provided sustained relief. She felt she would be condemned to a life of semi-invalidism.

Four months ago her doctor decided to try a "new drng that is producing dramatic results" in a number of joint pain and inflammatory conditions.

Mrs. C. M. took the drug, and within two weeks she was up and around—walking pretty much as though she had never suffered from arthritis of the hip. She's been comfortable and active ever since.

"I can't believe it," she declares. "This medicine is marvelous. I would call it a miracle."

Miracle or not, tens of thousands of patients throughout the United States and Europe, with a broad variety of physical ailments, are beginning to swear by the drug that is proving to have remarkable effects—in some cases within 36 to 72 hours.

The drug, largely unheralded and unpublicized until now, is called Indocin (indomethacin is its chemical name). Perhaps its most extraordinary quality is that it can relieve pain and inflammation caused by rheumatoid arthritis, gout, bursitis, arthritis of the hip, trick knee (usually the result of injured tendons and cartilage), "tennis elbow," and a host of other less common disorders characterized by pain and swelling in and around the joints.

Indocin is encouraging news if only because a estimated 12 million Americans suffer from arthritis and related joint disorders, and a good many of them—perhaps two million—cannot tolerate previously developed drugs, or such drugs have had little if any beneficial effect.

Actually, it is among many of these patients that Indocin is beginning to score its most impressive victories. These are individuals who have been "put on" almost every available drug—without lasting benefit.

Indocin, however, provides such dramatic relief for some of these patients—and so quickly—that many of them are moved to sit down and write about their experiences with the drug to its producer, Merck Sharp & Dohme of West Point, Pennsylvania.

The following are some samples of these letters to the pharmaceutical firm:

From Kansas City, Missouri: "I have had rheumatoid arthritis for 12 years. And I have taken many different medications. But for the first time—with Indocin—I'm free of pain. I'm no longer ornery. My wife says she's glad to have the old me back again. . . ."

From Minneapolis: "Because of bursitis I had to give up golf two years ago. But with your wonderful medicine I'm in good enough shape now to play golf once again. . . ."

From Detroit: "For five years the pain of my arthritis of the hip was unbearable. Now, with this drug of yours, I feel like a new person. Your Indocin is the best present anyone could have given me. . . ."

And from San Diego: "This is the first 'love letter' that I have ever written to a corporation. . . . After a very short period of taking Indocin, I can walk again without a cane. . . . I pray that you will realize fully the rewards that your splendid discovery so richly merits. . . ."

The "splendid discovery" actually took place several years ago at Merck Sharp & Dohme. Research workers there came upon a synthetic compound that had some surprising effects in animals. Not only could it reduce pain and inflammation but, given together with older pain killers, Indocin was found to reduce the need for these latter drugs.

This particular capability of Indocin is especially important. For in study after study, it has been found that if Indocin is given along with the corticosteroids (a commonly used "family" of anti-inflammation drugs), the need for these steroids gradually diminishes. This, in turn, can be invaluable, because very often when steroids are given for prolonged periods the side effects are worse than the disease itself.

Steroids are known to produce changes in body fluid balance and can cause weight gain, stomach upset, changes in contour of the face, and they are suspected of having adverse effects on vision.

The "steroid reduction" value of Indocin has been commented upon in scientific papers by a number of medical researchers. But one group from the University of Buffalo School of Medicine summed up the entire subject after studying more than 200 patients who were taking Indocin. The Buffalo group declared:

"At present 65.7 per cent of the patients have been improved for periods of six to 14 months. There has been a gradual decrease in the inflammatory indices, improvement in joint mobility and function. . . ."

One of the most interesting facets of indomethacin administration has been the ability to gradually reduce the amount of steroid therapy in patients who had been using these hormones for periods of three to eight years. . . .

"This effect is very gradual and sometimes difficult to ascertain but does occur in the majority of patients under prior steroid therapy. . . ."

The same effect has been noted—along with Indocin's other values—at other leading medical centers located at the University of Colorado, the University of Southern California, the University of Washington, and elsewhere throughout the nation.

Despite Indocin's dramatic effects in some cases and its increasing acceptance by even some of the most skeptical medical practitioners, a few facts should be borne in mind—facts that are indispensable to understanding the role of any drug—new or old.

All prescription drugs, Indocin included, have side effects—that is, they produce negative reactions, reactions that make the patient either mildly annoyed and anxious or profoundly distressed physically or mentally.

All prescription drugs, Indocin included, work for some patients and not for others. No drug is a universal cure-all. In arthritis and related joint diseases, the actual causes are not known—and therefore there are at present no available drug "cures." At best, the drug provides relief from the symptoms.

However, Indocin is a "new" drug—that is, it was approved for prescription use in 1965. Therefore, it has been subjected to extremely rigorous tests—tests that were not required of certain of the older anti-inflammatory drugs.

Within the past four years the Federal Food and Drug Administration, which is charged with approving—or disapproving—new prescription drug applications, has tightened the requirements leading to a new prescription drug being permitted on the market. Indocin has passed these new, much tougher standards.

Despite this, Indocin *does* have side effects—at least for some patients. And some patients get little if any therapeutic effect from the drug.

Here, in brief, is a rundown on the “minus” side of the Indocin ledger: Somewhere between ten and 25 per cent of the patients experience side effects. Some of these are mild, some are severe. Some patients experience headache, nausea, dizziness, and a few have intestinal bleeding. However, it is estimated that these effects are mild much of the time. Only an estimated ten to 15 per cent of the patients must give up the drug because of negative effects.

Says the Council on Drugs of the American Medical Association in a report not yet published: “With prolonged administration, ten per cent to 15 per cent of the patients who responded initially must stop taking indomethacin because of its untoward effects. . . .”

However, also within the AMA report, the following appears: “Indomethacin has been particularly useful in the treatment of . . . osteoarthritis of hip joint, a condition that is resistant to all other anti-inflammatory agents. . . .”

“Indomethacin produces anti-inflammatory effects in patients with gout. . . . It has produced relief in acute attacks within 48 hours.

“Because it lacks the untoward effects of colchicine [another anti-gout drug], some clinicians consider it to be the drug of choice for these attacks. . . .”

One of the most striking talents of Indocin lies in its ability to go to work quickly on the painful joint. Animal and human tests have shown that once Indocin is given, it reaches peak levels in the blood in just 30 minutes to two hours.

Thus, certain patients have begun to note relief from joint aches in two, three, six, or ten hours. One bursitis patient, for example, a 35-year-old executive from Hartsdale, New York, told his family doctor that once he took Indocin, “My shoulder began to feel better in just two or three hours. On just two Indocin capsules per day, I can feel pretty comfortable during an acute bursitis attack.”

A random sampling of a half-dozen doctors in various medical centers around the country produced the following assessments of Indocin:

1. When the drug works in a patient, the results are very dramatic. Relief comes quickly and may last for long periods.

2. In some patients, however, there are no beneficial effects at first. The drug must be continued for some weeks before it does any good at all.

3. Patients on Indocin should be watched very carefully for side effects. It has been reported that, following Indocin administration, some individuals have developed ulcers. However, it cannot be stated categorically that the drug had anything to do with the onset of this stomach ailment.

4. Somewhere around 75 to 80 per cent of all patients tolerate the drug well—and *most* of these patients experience real relief from symptoms.

5. Apparently, results are most remarkable among patients with arthritis of the hip, but many other patients with joint ailments do get dramatic relief in comparatively short periods.

Actually, the first human trials with Indocin started in November 1961. Since that time, more than 5,000 patients have been involved in worldwide studies of Indocin. Prior to the “patient-testing stage” more than 100,000 animal experiments were conducted by Merek to establish that the drug was potent and had worthwhile effects.

In those animal studies it was found that if researchers injected animals with a drug that itself could cause considerable inflammation, Indocin could reverse the inflammatory effects.

As is the case of so many other drugs, the exact mode of action of Indocin is not known. The same holds true for aspirin—the most widely used of all medications—and for penicillin—the miracle drug that has saved more lives than perhaps any other drug in the history of man. Doctors know that aspirin and penicillin work but are not exactly sure how they work. This is true, too, of Indocin.

Once it was established that Indocin could reduce inflammation, further tests indicated that its site of action must be within the inflamed joint itself. In addition, tests showed that its anti-pain capabilities at least equaled those of aspirin (which also is widely prescribed for arthritis) and in some instances exceeded the results aspirin could produce.

Interestingly, Indocin not only reaches peak levels in the blood quickly but it is eliminated from the body quickly, too. This is a distinct advantage, because pharmacologists (specialists interested in the chemistry of new drugs) are convinced that drugs that are quickly eliminated usually have a greater built-in safety factor. The feeling is that the quicker the drug gets in and then out of the body, the safer it is likely to be.

Studies show that Indocin may be eliminated entirely within 48 hours, which, as prescription drugs go, is extremely quick. There are, for example, some drugs on the market that remain in the body for several days, or even weeks, after initial administration.

During the clinical trials of Indocin the majority of patients treated were suffering from chronic joint disorders and related rheumatic diseases that had a "history" of at least five years' duration. Most of the patients selected for treatment had failed to get relief or had experienced serious side effects from other available drugs.

Thus, from the outset, Indocin was designed as a sort of "trouble-shooter" drug that could help patients who might not have gained beneficial effects from any other medication. There are, as a result, countless cases in the Merck files that show that Indocin works where no other drug has.

Whenever a new drug is introduced, doctors wonder whether it will have major effects on the body's vital systems. Indocin's record in this regard is good. Studies show that it has no significant effect on weight, pulse rate, or blood pressure. Nor does it upset the body's glandular system or its blood-clotting mechanisms.

Indocin's history is a fascinating story in itself. Research at Merck into Indocin-type compounds started about a decade ago, but Merck's interest in the entire subject of pain and inflammation goes back at least 30 years.

In 1933 Dr. R. E. Gruber, a Merck vice-president, agreed to a request made by the Johns Hopkins School of Medicine, Baltimore, to develop a process for producing adrenal cortex hormones for the relatively few sufferers of Addison's disease and other adrenal disorders.

Merck did this, and the spark of interest was rekindled during World War II when the company was asked to help Dr. Edward C. Kendall in research on adrenal hormones. Merck was told that this research "would be in the national interest."

It seems that during the war American intelligence had heard rumors that Germany was buying adrenal gland extract from Argentine slaughterhouses and giving it to Luftwaffe pilots in the hope that the extract would enable the pilots to fly at altitudes of 40,000 feet or more.

Obviously, the United States military wanted to know if adrenal extract conferred any such capability upon airmen. (It didn't.) Dr. Kendall went to work with a young Merck chemist, Dr. Lewis H. Sarett, who, in 1944, just before turning 27, developed the first synthesis of compound E. This development, in turn, paved the way for the discovery that compound E had therapeutic effects. The compound then became known as cortisone.

After the war cortisone and its later modifications came into wide use for arthritis and other inflammatory ailments, but gradually it was discovered that cortisone produced a great many undesirable side effects.

Thus, from the early 1950s until the present, researchers have been hard at work trying to develop anti-inflammation drugs that work but do not produce cortisone-like side effects.

In 1953 a Merck research group, led by Dr. Sarett, began to wonder if they could develop a drug that was nonhormonal in nature, and thus unlike cortisone, but a drug that would provide the same benefits as cortisone.

In their search they worked on compounds at first thought to be valuable against certain emotional disorders. But the compounds later proved to be of very limited value in mental disease. One of the compounds screened, however, did have some positive effects on inflammation, and this in turn led to the synthesis of still another chemical. In March 1964 this chemical, indomethacin, became, in the words of one well-known scientist, "the most promising drug since cortisone."

After considerable testing, the drug was approved for prescription use in June 1965. Merck has deliberately avoided publicity for the drug for several reasons.

Since the FDA's new tough line on all new drugs, pharmaceutical companies are becoming reluctant to blow their horns about any new compound. And more

important, Indocin is designed to relieve symptoms of chronic disorders—illnesses that come and go or come and stay for years on end.

The company has been under standably reluctant to sound the trumpets about Indocin until it had at least a year's experience with the drug on the prescription market. Now, with patients receiving lasting benefit from Indocin, Merek feels it can begin to bring some aspects of the story of the drug to the public. The drug is proving itself to even the most conservative physicians and laboratory scientists.

Of course, each day the line of grateful Indocin patients becomes longer and longer. The drug does not have to prove itself to these people. It already has been a "lifesaver" to thousands.

There is, for example, the 62-year-old New York City carpenter who could not work for nine years. His hands were so crippled by arthritis that he could not hold his tools. After five weeks on Indocin his hands improved markedly.

"I can hold a hammer again, and what's more, I can drive a nail—pretty straight, too," he says.

Within a few months this man expects to be back at work. Indocin will have returned him to a reasonable level of personal dignity—not to mention to a reasonable level of income.

But perhaps the most extraordinary Indocin success story of all involves a 68-year-old Connecticut woman who has been a virtual invalid for the past eight years. Her arthritis was so bad that years ago she gave up going to the corner grocer for the absolute kitchen necessities.

"After I began to take Indocin," she relates, "I noticed that I felt better. It was only a couple of days or so that I'd been taking the drug, but I began to feel better. After a few weeks I felt that I could actually take a little walk—perhaps down to the front of the house and back."

Last week she walked about 60 yards to the corner grocer. When she left, still somewhat unsure of herself, though not in great pain, she was sobbing just a little bit. But it was a joyous cry.

**Dr. McCLEERY.** The story, written by two science writers, in the July issue featured Indocin by name in the title of the article, and said it was useful for "bursitis," "trick knee," "tennis elbow," and "a host of other less common disorders characterized by pain and swelling in and around the joints." The support for these claims was largely lay testimonials some of which, according to the article and the firm, were made available to the writers by the sponsor of the drug.

Mr. Fletcher said that the firm was in no way responsible for the article, that the authors had heard of stories about the drug from a variety of sources and wanted to do an article about it, and that the firm had simply responded to this inquiry from responsible science writers. Mr. Fletcher said the article was in no way promotional and wanted to so assure the agency.

The drug, of course, had not been approved for use for the above-mentioned conditions for which it was claimed to be effective in the Pageant article. We knew also that a popular article of this sort is apt to create a demand for the drug by the patients who read it.

**Senator NELSON.** As I understand from your testimony at the top of page 2, this article for Pageant magazine was submitted to the FDA prior to publication?

**Dr. McCLEERY.** Yes, sir.

**Senator NELSON.** So there wouldn't be any question about what was in the article, and FDA could, at least, express their disagreement with claims made for the drug to Pageant magazine if they desired.

**Dr. McCLEERY.** That is right. I believe that the time interval from the submission of the letter, which was to Mr. Cron—that at that time we would have to assume that the article was already in press, although not yet mailed in the July issue. And again, it was, without any question in our minds, an article actually written by the authors

who were independent, I guess well known, science writers in their field. So it was their article in substance, and not that of Merck & Co., so far as we know.

Senator NELSON. But they had advance copies of it.

Dr. McCLEERY. Yes.

My office, the Division of Medical Advertising in the Bureau of Medicine, was asked to review the article for possible violation of the law, and to review also the advertising of this drug in medical journals to determine if the drug was being promoted to the medical profession on the basis of unapproved claims?

Our concern was that if the firm would make these data on unauthorized uses available to a free-lance team of writers, it might not be scrupulous in its advertising to the medical profession.

I would like to leave this now and go to the performance of the company—

Mr. GORDON. What did your Division do about this article?

Dr. McCLEERY. We responded to the internal inquiry from the office of Mr. Cron and gave our view of what the article in fact was, and we wrote a report of the deficiencies which we thought the Pageant article contained and what our opinion was of whether or not the law might be considered to have been violated by Merck & Co. as a consequence of this article.

Mr. GORDON. And what was your opinion about that? Did you think the law had been violated?

Dr. McCLEERY. Yes. Our opinion in the Division of Medical Advertising—which I would like to ask Mr. Goodrich to follow up on—our opinion of whether the law in fact had been violated, I have some apology for. But we thought that the law had been violated because the article, in the form it took, could be considered to have been caused to be issued by the company because of the turning over of documents to the writers which were built into the article and which would have come from no other source. And for this reason, the promotion of unauthorized, unapproved uses, which could be a consequence of the article, we thought should be laid to the door of the company.

Senator NELSON. Well, now, this article was published in the July 1966 issue of Pageant.

Dr. McCLEERY. Yes, sir.

Senator NELSON. I notice that in a letter dated March 8 of this year, 1968, you concur in the recommendation for prosecution of the company.

Dr. McCLEERY. That is true.

Senator NELSON. And that on March 11, 1968, Dr. Ley stated, "The Bureau of Medicine recommends that prosecution of the firm be instituted subject to approval by the Attorney General." What is the status of that recommendation now?

Dr. McCLEERY. I think Mr. Goodrich can speak better to that.

Mr. GOODRICH. The case is in my office.

Senator NELSON. But the recommendation has not left your office.

Mr. GOODRICH. It has not.

Senator NELSON. Is it correct that the prosecution involved not only the Pageant article, but also some other advertising materials?

Mr. GOODRICH. Yes, sir.

**Senator NELSON.** There are several documents here as well as letters by Dr. Weinstein, Dr. Ley, Dr. McCleery, and others; and since they explain this situation in some detail, and specify the kinds of violations that the FDA believes do occur, and give examples of them, I would ask that they be printed in the record at the appropriate place.<sup>1</sup>

**Dr. McCLEERY.** I would like to turn now to the third element of the promotional campaign with which we had to deal, and that concerns the medical journal advertising to the medical profession by Merck Sharp & Dohme.

We have already supplied for the record copies of two major kinds of ads<sup>2</sup> which have been used by the company, one characterized by a submission which you have in your hands dated July 18, and which is identical in content to the issues of the same ad in July 4 and August 15, 1966, issues of the Journal of the American Medical Association. There is a second ad, with some minor changes, which you also have a copy of, and bears a handwritten inscription called the "The" Ad, which was published in November 1966, and I want to make comments on both ads.

**Mr. GORDON.** Which ones are these?

**Dr. McCLEERY.** The first ad, you have a copy of the JAMA dated July 18, 1966. We happened to act in our memos on an issue dated July 4. All of these ads are identical. They are just prints of the same ad in different issues. The one you have at hand is marked with the hand inscription "A." The "A" ad is July 18, 1966. As I go along, we will deal with the features which are common to the second ad, marked November 1966, in the American Journal of Medicine.

**Senator NELSON.** Are you referring now to the AMA Journal?

**Dr. McCLEERY.** Right.

**Senator NELSON.** In looking at the ad, it shows a radiograph of a left foot and says, "Indomethacin is a drug of choice in acute gout." Is that correct?

**Dr. McCLEERY.** Are you reading correctly?

**Senator NELSON.** "Indocin is a drug of choice in acute gout."

**Dr. McCLEERY.** I just wonder what your question is.

**Senator NELSON.** Is it a drug of choice, do you know?

**Dr. McCLEERY.** One of the reasons we have submitted both this ad and the ad of November is because the author said "the drug of choice." You will note in the JAMA ad there is a bracket around the "a" which the company at this time inserted in place of the author's own statement that it was the drug of choice.

**Senator NELSON.** Who inserted the "a"?

**Dr. McCLEERY.** The company and its advertising agency. We have assumed this was in a mood of good instinct and caution that the company changed the author's quote from the word "the" which is correct, and which is in the view of many a far less defensible statement concerning the value of the drug. The complexities of what the statement says with the word "a" in instead of "the" is the problem. In any event, in answer to your question, in my opinion, and in the opinion of many who are expert in this field which I am not, indomethacin is a good drug for the treatment of acute gout—it had not reached the level of "the drug of choice" for acute gout.

<sup>1</sup> See documents and letters beginning at p. 3246, infra.

<sup>2</sup> See supplemental information beginning at p. 3221, infra.

Senator NELSON. It had reached the level of the drug of choice?

Dr. McCLEERY. That it had reached the level of "the drug of choice" at that time I think hardly anyone would accept—perhaps the authors would, but most would not agree that even today it is the drug of choice.

Senator NELSON. They would not agree today that it is the drug of choice.

Dr. McCLEERY. I believe not. That it is a good drug, yes. But there is no evidence that exists on any scientific basis of comparative studies with Indocin and other drugs used in the treatment of gout. The kinds of studies that would be required to make an acceptable statement that this is the drug of choice have not yet been done.

Senator NELSON. The phrase "the drug of choice" are words of art, aren't they, in the medical profession? That is, they have a special meaning. When you say "the drug of choice," those are words of art in medical language, are they not?

Dr. McCLEERY. I would be more inclined to say that the company's use of the word "a" puts it into more the realm of art and not of science.

Senator NELSON. I was using a legal phrase. I meant to say the phrase has a special meaning to the medical profession if you say a drug is "the drug of choice," does it not?

Dr. McCLEERY. I would say that the phrase "the drug of choice" should be based on science, and not on art.

Senator NELSON. I am confusing you. I am using a legal phrase, so we will just skip that. The phrase "the drug of choice" has a special meaning in medical language.

Dr. McCLEERY. Yes.

Senator NELSON. That is what words of art mean in legal phraseology. And what is the meaning of that phrase "the drug of choice" in medicine?

Dr. McCLEERY. If one takes at face value the claim, and believes that the person making such a statement is to be believed, it is the highest accolade that one can give a drug in competition with other drugs used for the same treatment—that is the best drug, and it is the drug that should be chosen for the treatment of most cases—should be tried first if one is choosing from a number of drugs.

Senator NELSON. That is my point. If you say "the drug of choice" you mean that it is the first drug recommended to be tried, based upon all the scientific evidence that is available as of that time; is that correct?

Dr. McCLEERY. Yes.

Senator NELSON. I had to read it twice before I saw the "a" in parenthesis. If you glance at this as I do you see "indomethacin, drug of choice for acute gout." This is this kind of very clever advertising which, it seems to me, can be very misleading. Isn't it easy enough to read something like that ad and not notice the little "a" in parenthesis. You simply see "drug of choice," and interpret it to mean automatically, as medical people would, that this must be the drug of choice?

Dr. McCLEERY. You put me in the difficult position of defending the company, Senator, and I do not welcome it. But I must say that in our discussions with the members of the firm, they affirmed, and I for one believe, that their reason for putting in the word "a" was

that they were queasy about claiming it was "the" drug of choice, and this, in their mind, was to weaken the impact of the claim, and I believe they were telling the truth.

Senator NELSON. It is weaker than "the drug of choice." But why use the phrase "drug of choice" which are words of art to the medical profession unless you are trying to give the impression to somebody who glances at it that it is the drug of choice? I read all kinds of these ads. If you sit and analyze them long enough, carefully enough, you can end up defending them. But that is not the way people read ads.

Dr. McCLEERY. No, sir; but I think there is more of interest on this point than we have gotten to, and I direct your attention to the use of "a" in two other places in the same ad. If you start on your left, I believe you will see another quotation from the paper by the same authors in reference to rheumatoid arthritis. At that point you will see the use of the word "a" in brackets again inserted into the quote. The article actually said at that point this is "the first noncorticosteroid drug" to do what follows. And the company again removed the words "the first" and inserted in caution and I would say good instincts, regardless of other attributes of the ad, the word "a." You will find it again in the third panel, in a quote from, not a paper, but remarks at a symposium sponsored by Merck & Co., by a Dr. Englund of Phoenix, Ariz., where his quote is changed to include the word "a" in the body of it. Do you see that?

Senator NELSON. I see it. And if I understand what drug of choice means, I am impressed by the fact that every time the company can use the phrase "drug of choice" it is there. Why don't they say a useful drug?

What would FDA say if under the reproduction of this radiograph of the foot it said "indomethacin is a", and then in capital letters "drug of choice," and then back to lower case, "in acute gout."

Dr. McCLEERY. We would have said it is very little worse than we thought it was in its present form.

Senator NELSON. You would say it was very little what?

Dr. McCLEERY. Very little worse. I say it is bad the way it is. What you suggest would make it very little worse. It is bad enough.

Senator NELSON. These are words of art in the medical profession, so every time the words can be fitted in, the phrase "drug of choice," which captures any medical person's eye, the phrase is used. Then to technically clear themselves they add a little "a" with a bracket around it.

Dr. McCLEERY. Yes, sir. We felt it was wrong, and the use of the word "a" in the insertion did not relieve them of the fault. We charged the ad as misleading in its JAMA form. I would only like to point out to you that you also have an ad which we labeled the "The" ad, which is a November 1966 issue. There the ad that you see appears in all of its glory with the quotes intact, so that the word "the" is in all of the places where the word "a" is here. And these are the two ads that I want to discuss in detail this morning.

Senator NELSON. All right. Thank you.

These ads will be put in the record in the appropriate place.

Are you going to get to the October 24 issue of Modern Medicine, which carried almost the same ad as the Journal of the American Medical Association, again where they say it is the drug of choice?

Dr. McCLEERY. Yes, sir. The reason we submitted that little magazine,

in its October issue is to show the breadth of the November 1966 campaign containing the word "the" in place of "a," and you have copies of the October 26, I believe, issues of Modern Medicine, you also have copies of the November 1966 issues of the American Journal of Medicine, and Arthritis and Rheumatism magazine, all of which are the same. They are just prints of the same ad in different journals.

Senator NELSON. Did the package insert at any time include the same phrasing, "the drug of choice"?

Dr. McCLEERY. No, sir; it did not.

Senator NELSON. And the FDA did approve the package insert? So at the same time that the package insert is making a lesser claim, using different language, the company is running advertisements in the Journal of the American Medical Association and other medical magazines claiming that Indocin was the drug of choice in gout; is that correct?

Dr. McCLEERY. Correct.

Senator NELSON. So there was no question that the company knew what the viewpoint of FDA was as to the requirements for the package insert at the time they were running these ads in the medical journals.

Dr. McCLEERY. I should say not.

The so-called A ads that we have been discussing appears as identical advertisements in the Journal of the American Medical Association in many issues, but also in issues of July 4 and August 15. And these were found to be featuring under the major headline the theme that the drug "extends the margin of safety in the long-term management of arthritic disorders." At the same time—

Senator NELSON. Where are you, Doctor?

Dr. McCLEERY. The middle of page 3.

Senator NELSON. Please proceed.

Dr. McCLEERY. At the same time, the Office of Marketed Drugs, under Dr. Jennings, who appeared yesterday, was negotiating with Merck for changes in the package labeling to emphasize newly recognized hazards that had emerged during the first year of clinical experience since original approval of the drug.

The JAMA ads in July 4 and August 15, 1966, issues were analyzed and found to be defective, in our opinion, in several respects. I am going to mention only a few of them. I would not want you to believe we have exhausted our objections by what I point out today.

Senator NELSON. This is now in what edition of JAMA?

Dr. McCLEERY. The July 18 issue that you have in front of you.

Senator NELSON. That is the one you are going to discuss now?

Dr. McCLEERY. Yes, sir. I would like first to mention generally the major defects of the ad in our view, and then will be more specific regarding the details of our objections to certain of the features of this and of a later ad which appeared among others in the November 1966 issue of the American Journal of Medicine.

The basic theme of greater long-term safety in the ads was not supported by the clinical experience.

Mr. GORDON. You say "greater"?

Dr. McCLEERY. It is a kind of advertising technique which has a great deal of value because it says "greater" but does not specify greater than what, and goes in the advertising world under the delight-

ful phrase called a "dangling comparative." And this is represented well by this headline.

Senator NELSON. You are referring to the headline that reads "extends the margin of safety in long-term management of arthritic disorders"?

Dr. McCLEERY. Yes.

This implies that the drug, as a theme of advertising, has greater long-term safety than something else, or in effect, in our view, everything else.

To the contrary, in our experience the longer the drug had been on the market, the more serious adverse experience information had been reported to us.

Now, the ad, as you have seen, and talked about, used four blocks of depictions of X-rays that were accurate representations of the four indications for the drug. And they quoted underneath these depictions, and in support, presumably, if the ad were a good ad—in support of the headline claim. And they quoted apparently authoritative sources, but without the full impact of the limited experience contained in the actual articles they were quoting. And the ad features, for example, one reference which on checking proved to be only a 2- or 3-inch abstract of a 1964 speech. That is the one on the second block by Dr. Rothermich.

The ad quoted the author's opinion that "results have been uniformly excellent or good." Dr. Rothermich's same abstract, although brief, also included his view that while "excellent results have also been obtained in some cases of rheumatoid arthritis, there have been striking failures as well." So it is perhaps not surprising that while the advertising included this author's favorable remark regarding his experience with spondylitis, which they did, they then turned to another author, namely Hart and Boardman for a more favorable quote concerning the possible value of the drug on rheumatoid arthritis, and did not reflect Dr. Rothermich's view on rheumatoid arthritis in the ad. We consider this as not quite cricket, at least.

It offered the drug for "arthritic disorders," rather than solely for the specific four conditions for which it has been approved.

This is a small point, and one of the kind of things we have been accused of "nit-picking" about. All we would have asked here was they merely put in the word "certain," to show the reader when he was getting a quick view of what the drug was for, that this was not for all arthritic disorders, but at least only for certain of them. And then he would look more carefully as to what he expected the drug to be indicated for.

Senator NELSON. Did the company object to the insertion of the word "certain"?

Dr. McCLEERY. Well, we met them somewhat later than this time. Whereas I am not sure whether they objected or not, there was a marked change in their advertising subsequent to our meeting, so that this became an issue of no importance, because all of these claims disappeared subsequently.

The ad goes on in a major way to characterize the drug as non-steroid, which of course it is, but failed to disclose in this connection that whereas it was not a corticosteroid, which is a class of drugs also used for the treatment of these conditions, and for which there are major side-effect concerns already well established in the minds of

the profession—so they failed to disclose in this connection that Indocin has some of the major side effects of these steroids themselves—for example, an ulcer-producing effect.

The ad goes on to claim that the drug extended the margin of long-term safety without any evidence in our view to support the claim, and it quoted from isolated pieces of literature to support this—one an excerpt from a symposium sponsored by the company—and to claim that the drug was “the drug of choice” in gout and in osteoarthritis of the hip, neither of which claims had been approved for inclusion in the package labeling of the drug.

It also quoted from two leading English authorities to the effect that the drug was useful in most cases of rheumatoid arthritis, when these authors had used the tablet and not the marketed capsule, and when their actual opinion, known to Merck, was that the drug was useful in only selected cases of rheumatoid arthritis.

It featured the claim of one of the participants in a Merck-sponsored symposium. This is attributed to Dr. Englund—they featured a claim, quoting from him at this symposium, that he had had 500 patients on the drug for 3 years, when Merck’s own records would have told them this was not true.

And finally, in the “brief summary” of information on side effects and contraindications, some of the major warning information was left out, such as the fact that indomethacin itself had caused ulcers of the stomach and so on, and that the drug should not be administered to children.

Now, how they did this is a very interesting operation—

**Senator NELSON.** Which ads were they? In which ads were the two warnings left out?

**Dr. McCLEERY.** They were left out in both of the ads. Most of these features that I have been discussing are common to the July ads and the November ads, Senator. You see at the bottom of the page of the ad that you have in front of you what we call “the brief summary,” and it contains information from the package insert that summarizes the warning information on the product. We say that, in practical fact, they had left out significant warnings which they are required to include in that brief summary of warning information.

Because it is a very subtle, but very important, advertising kind of language—I would like to point out why we say this.

**Senator NELSON.** You are saying that in no place in the fine print of this ad do they include the warnings that indomethacin may cause ulcers, and that the drug should not be administered to children.

**Dr. McCLEERY.** Yes, sir.

**Senator NELSON.** And that was well known at that time, was it not?

**Dr. McCLEERY.** Yes. But the issue is much more subtle, because there are references to both of these subjects in the ad which we have found fault with, and I would like to stress this kind of advertising technique which appears to fulfill the requirements of law, but in our view does not, because it is a very common practice, one which we are trying to fight. It is often called nit-picking by our opponents, as a way to denigrate the significance of changes in words, which we think is very important.

**Senator NELSON.** I have not read all the fine print. Are you saying that in this JAMA ad of July 18, 1966, somewhere in the fine print, there is the warning that it should not be used for children?

**Dr. McCLEERY.** I am saying that in our view it is not, although the subject is discussed. I would like, if I can go on just for a moment, to point your attention to the way that the ad differs from the package insert in these respects.

We believe that these that follow exemplify what might be called the euphemistic style of revealing warning information. The ad's "brief summary" translated the package insert's warning "Indocin itself may cause peptic ulceration \* \* \*" into the area of causal doubt in this manner: "Ulceration of the stomach, duodenum, or small intestine have been reported. \* \* \*"

**Senator NELSON.** I do not see that in the ad. Is that the July 18 ad?

**Dr. McCLEERY.** Yes, under the "Precautions." "Ulceration of the stomach, duodenum, or small intestine have been reported."

**Senator NELSON.** Is this under the warning section in the package insert?

**Dr. McCLEERY.** It is under the contraindications section—but it is in the ad's precaution section. Under the contraindications section in the package insert is the statement that I read first, which is a plain statement which carries the idea that the company has agreed with the Bureau of Medicine to say "Indocin itself may cause peptic ulceration." We are saying that in no way is that statement in the package insert properly reported to the physician in the ad by the statement "Ulceration has been reported." This is a style of statement about side effects that is traditional in ads over the years. It only means that many side effects are reported to be associated with the use of a drug, which may be by chance, and to say merely that it has "been reported" in no way suggests that it is "caused by" the drug in question. On the other hand, the package insert is very clear.

**Senator NELSON.** Where does this precaution appear in the package insert?

**Dr. McCLEERY.** Under the contraindications section. It is a piece of information under the contraindications section.

**Senator NELSON.** It does not appear under the warning section?

**Dr. McCLEERY.** I cannot tell you whether it also appears in the warning section. But it does appear in the package insert in the contraindications section.

**Senator NELSON.** There is also a warning section in the package insert, isn't there?

**Dr. McCLEERY.** Yes.

**Senator NELSON.** Those warnings do not appear in the warning section of the package insert?

**Dr. McCLEERY.** I frankly cannot tell you. I do not know that well enough by heart.

**Senator NELSON.** I wish you to submit for the record the package insert that was being used by the company at that time. I would like to have that in the record at this stage of the testimony.

(The information to be furnished for the record follows:)

DIRECTION CIRCULAR

INDOGEN<sup>®</sup>  
INDOGEN  
(INDOMETHACIN)



MERCK & SHARP & DOHME  
Division of Merck & Co., Inc.  
West Point, Pennsylvania



MERCK & SHARP & DOHME

A.H.F.S. Category: 92:00  
Ph. 262401 Effective May 1965 Printed in U.S.A.

INDOCIN®  
(indomethacin)

INDOCIN® (indomethacin) is a new "anti-rheumatic" drug that has anti-inflammatory, analgesic, and antipyretic activity. It has a unique chemical structure which differentiates it from the salicylates, corticosteroids, phenylbutazone-like compounds, and colchicine. Unlike corticosteroids, it has no effect on pituitary or adrenal function.

INDOCIN is an effective anti-inflammatory agent that is suitable for long term as well as short term use in adult patients of all ages. It has been found effective to relieve pain, reduce fever, swelling, and tenderness; and increase mobility in patients with rheumatic disorders.

## INDICATIONS

INDOCIN has been found effective in the treatment of:

Rheumatoid arthritis

Rheumatoid (ankylosing) spondylitis  
Degenerative joint disease (osteoarthritis) of the hip

Gout

In these conditions INDOCIN may often replace other commonly used agents such as corticosteroids, salicylates, phenylbutazone-like compounds, and colchicine.

## Rheumatoid Arthritis

In many patients with chronic rheumatoid arthritis INDOCIN produces a significant decrease of pain and stiffness within 48 hours, while in other patients treatment must be continued longer before significant subjective relief or objective evidence of decreased joint swelling and tenderness occurs. Treatment with INDOCIN should be continued for at least a month before concluding that it has not produced significant benefit.

When a response to INDOCIN has been obtained, the daily salicylate requirements can usually be reduced and often stopped. Also, if patients have been receiving corticosteroids, the steroid dosage often can be gradually reduced by 25 to 50 per cent, and in some patients it can eventually be completely discontinued. In such instances the steroid dosage should be reduced slowly.

In acute rheumatoid arthritis, or in acute flares of chronic rheumatoid arthritis, INDOCIN will usually produce prompt improvement with relief of pain, tenderness, swelling and stiffness.

## Rheumatoid (Ankylosing) Spondylitis

INDOCIN frequently produces marked relief of pain and improved motion of the spine within 3 to 10 days.

INDOCIN®  
(Indomethacin)

titis, pruritus, urticaria, angioneurotic edema, skin rashes, and edema.

Extensive laboratory examinations have been made during treatment with INDOCIN. A slight, usually transient, increase in BUN has been reported in some patients. Although two investigators have reported apparent changes in renal function, the reliability of the techniques used was uncertain. The preponderance of evidence indicates that INDOCIN does not have an adverse effect on renal function. Nevertheless, renal function should be checked periodically in patients on long term therapy. Patients with pre-existing renal disease have received INDOCIN without difficulty.

A few cases of leukopenia have been reported in patients with rheumatoïd arthritis; leukopenia is not uncommon in this disease. Transient elevations in alkaline phosphatase, cephalin-cholesterol flocculation, and thymol turbidity tests have been observed in some patients and, rarely, elevations of SGOT values. The relationship of these changes to the drug, if any, has not been established.

Unlike steroids, INDOCIN has not been associated with an increased incidence of infections. As with any new drug, patients should be followed carefully to detect unusual manifestations of drug sensitivity.

#### DOSAGE AND ADMINISTRATION

INDOCIN is available as 25 mg. capsules for oral use.

In chronic disorders treatment should be started with a dosage of 25 mg. two or three times a day. Starting therapy with low doses, with gradual increases when necessary, will produce maximum benefit and minimize adverse reactions. Always give INDOCIN with food or immediately after meals to reduce gastric irritation.

#### Dosage Recommendations for:

##### 1. Rheumatoïd arthritis and rheumatoïd (ankylosing) spondylitis

*Initial dosage:* 25 mg. two or three times a day. If the response is not adequate, increase the daily dosage by 25 mg. at about weekly intervals until a satisfactory response is obtained or a dosage of 150 to 200 mg. a day is reached. If a satisfactory response is not obtained with 200 mg. a day, larger doses probably will not be effective.

If adverse reactions develop as the dosage is increased, decrease to a tolerated level and maintain at that dosage for 3 to 4 weeks. If an adequate response has not then been obtained, gradually increase the daily dosage by 25 mg.

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at about weekly intervals to 150 to 200 mg. a day.

For patients with acute rheumatoid arthritis or with acute flares of chronic rheumatoid arthritis, increase the dosage daily by 25 mg. until a satisfactory response is obtained or a total daily dosage of 150 to 200 mg. is reached. If adverse effects develop as the dosage is increased, it should be reduced to a tolerated level for 2 or 3 days and then gradually increased by 25 mg. every few days as tolerated.

After the acute phase is under control, it is often possible to reduce the daily dosage of INDOCIN gradually to 75 to 100 mg.

*Reduction of steroid dosage:* Use of INDOCIN often will permit a gradual reduction of steroid dosage by 25 to 50 per cent. In some patients steroids can be slowly discontinued over a period of several weeks or months. The usual precautions should be observed in withdrawing steroids.

## 2. Degenerative Joint Disease (Osteoarthritis) of the Hip

*Initial dosage:* 25 mg. two or three times a day. If the response is not adequate, increase the daily dosage by 25 mg. at about weekly intervals until a satisfactory response is ob-

tained or a dosage of 150 to 200 mg. a day is reached. If a satisfactory response is not obtained with 200 mg. a day, larger doses will probably not be effective.

If adverse reactions develop as the dosage is increased, decrease to a tolerated level and maintain at that dosage for 3 to 4 weeks. If an adequate response has not then been obtained, gradually increase the daily dosage by 25 mg. at about weekly intervals to 150 to 200 mg. a day.

## 3. Gout

*To control acute attacks:* 50 mg. three times a day until all signs and symptoms subside. Definite relief of pain has been reported within 2 to 4 hours. Tenderness and heat usually subside in 24 to 36 hours, and swelling gradually disappears in 3 to 5 days.

*To prevent acute attacks:* During the interval phase of gouty arthritis the dosage may be reduced to as little as 25 mg. twice a day, given with an adequate dose of a uricosuric agent such as probenecid.

## CHEMISTRY AND PHARMACOLOGY

The chemical name for indomethacin is 1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-

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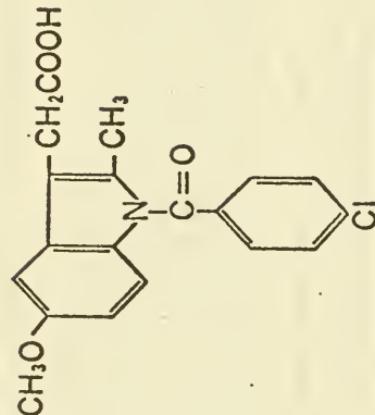
thymus, or retard gain in body weight. Its anti-inflammatory activity does not depend upon activation of the adrenals, since it was fully active in adrenalectomized rats.

The anti-inflammatory activity of INDOCIN was also demonstrated by its ability to inhibit edema formation induced by subplantar injection of carrageenin in rats. By this test, the relative potency of indomethacin was: 30 times aspirin, 20 times phenylbutazone, and 2 times hydrocortisone. INDOCIN does not possess antihistaminic or antiserotonin activity, since it did not affect edema induced by injection of egg white, serotonin, or yeast. Combinations of indomethacin and a steroid were more effective than comparable doses of either drug alone in inhibiting granuloma growth or edema formation.

*Antipyretic Activity*

INDOCIN is an antipyretic in laboratory animals. In rabbits it was about 20 times as potent as phenylbutazone and 10 times as potent as aminopyrine. Its duration of action was much longer than that of aminopyrine and comparable to that of phenylbutazone. In rats indomethacin appeared to be about 10 times as potent as phenylbutazone.

The antipyretic activity of INDOCIN has been

*Anti-Inflammatory Action*

In laboratory animals, INDOCIN is a potent anti-inflammatory compound. Results of granuloma inhibition tests in rats receiving the compound either orally or by local application indicated activity about 85 times that of phenylbutazone. Given orally, the compound was about 4 times as active as hydrocortisone. When given in effective doses to intact rats, indomethacin, unlike anti-inflammatory steroids, did not affect the size of the adrenals or

INDOCIN®  
(Indomethacin)

confirmed clinically by observations in patients with Hodgkin's disease, acute rheumatic fever, and a variety of other acute febrile conditions.

#### Analgesic Activity

Laboratory tests designed to detect mild analgesic activity indicate that indomethacin is more potent than aspirin or aminopyrine.

#### Absorption and Excretion

INDOCIN is well absorbed after oral administration in all animals, including man. In dogs, monkeys, rats, and man, peak plasma levels after an oral dose occur within 0.5 to 2 hours. The drug present in the plasma of dog and man is virtually all unchanged indomethacin, but a metabolite (probably the glucuronide conjugate) may be present for the first half hour after intravenous injection in the guinea pig.

The route of excretion is related to the species of animal and is independent of the route of administration or size of dose. Nearly all the compound could be recovered in urine and feces. The rabbit eliminates indomethacin almost entirely in the urine, while the dog excretes nearly all the compound in the feces. The rat, guinea pig, monkey, and man eliminate it by both routes. In man, about two-thirds of the drug is excreted in the urine.

In rabbits, rats, guinea pigs, and monkeys, some indomethacin is metabolized by deacetylation or demethylation and the metabolites are excreted in the urine as such or as the glucuronide conjugate. In man, however, no evidence of molecular breakdown has been observed, and virtually all of the material excreted in the urine is indomethacin glucuronide.

#### AVAILABILITY

No. 3316—INDOCIN capsules, 25 mg. each, are opaque blue and white, imprinted with an MSD trademark and potency, and are supplied in bottles of 100.

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Senator NELSON. Now, is there any place in this ad where the warning or precautions is made that it is not to be used in the treatment of children?

Dr. McCLEERY. Yes.

Senator NELSON. Where is that?

Dr. McCLEERY. The statement in the package insert is the one that was under considerable discussion yesterday, but includes among other verbiage the statement that the drug should not be administered to children. Those words are contained in the original package insert for the drug, under the contraindications section.

Senator NELSON. Are those the exact words? What are the exact words in the package insert?

Dr. McCLEERY. That the drug shall not be administered to children. That is in the contraindications section.

Senator NELSON. And is some reference made to that under contraindications in this ad?

Dr. McCLEERY. Yes. In the ad it is transformed into another style of transmitting information, and in the ad you will find near the bottom of the contraindications section the statement "safety in pregnancy and pediatric age groups has not been established." That is the only reference to children in the ad.

Senator NELSON. So instead of saying it should not be administered to children, as it says in the package insert, as required by the FDA, in the ad it says "safety in pregnancy and in pediatric age groups has not been established."

Dr. McCLEERY. That is right.

Senator NELSON. You consider that to be a much weaker cautionary statement.

Dr. McCLEERY. Yes, I do. I consider it is not the same information. Deficiencies in the ads were publicly noted in a speech before the Pharmaceutical Advertising Club in New York, on October 20, 1966, by our General Counsel, Mr. Goodrich. The firm quickly protested, and shortly thereafter on November 11, 1966, a sort of "Armistice Day," the firm's principal officers met with Dr. Goddard and his staff to go over the problem. The problem took into account all of the elements of the advertising that we have discussed.

At that meeting, the firm reported that on hearing Mr. Goodrich's comments in New York concerning Indocin advertising, that it had immediately ordered that ad discontinued, and was taking a close look at all of its promotional efforts.

Later on, not too much later, its physician and counsel responsible in the area of advertising came down to go over some ads for other products, that Merck makes and advertises, with us. And I must say in defense of the company that from that point in time on, they have behaved in a very exemplary way. We have watched their advertising on Indocin carefully subsequent to this point. We have watched their advertising on a number of their products for tranquilizers and anti-depressants. We have seen them introduce two major new products subsequent to the meeting in Dr. Goddard's office, and we could find no serious objection to those. And so I am glad to say this concerning the performance of Merck & Co. And I regret I cannot say it very broadly concerning a number of other companies with which we have dealt.

Senator NELSON. I am glad to hear that the Merck Co. is now co-operating in their advertising. But something puzzles me about it. This is from a letter of March 8, 1968, signed by you. Maybe you will want to look at it. But quoting from your letter, it says "Attitude of the firm. The poor attitude of Merck regarding the advertising regulations has persisted since their promulgation. This is clearly shown in the following pages from Attorney Colburn's letter." And then there are some quotes. Then you say, "In effect, Merck challenges all of the principles of fair balance provided in the existing regulations, and even challenges the Government's authority in respect to requiring ingredient information in advertisements except as specified in section 502(n)," and so forth and so on.

How does this letter dated March 8 conform to your present statement that they are cooperating in every way?

Dr. McCLEERY. It does seem contradictory, doesn't it?

Senator NELSON. A little bit.

Dr. McCLEERY. I hope that is not a letter, because I do not like to write letters.

Senator NELSON. I will show it to you.

Dr. McCLEERY. I am well aware of it, Senator. It is an internal memo.

Senator NELSON. Yes.

Dr. McCLEERY. What I said before—

Senator NELSON. Is the attitude internally different from what it is externally?

Dr. McCLEERY. No. I hope without looking at it I won't contradict what I said in that memo at least. What I said was, Senator, what Merck has done in reference to conforming to the law and the regulations—you did not ask, and I did not feel it necessary to say, what I think they think, why they are doing it, or what they think of our view of the law on proper advertising. So there is no contradiction.

Senator NELSON. I see. What you are saying is that they have made some changes in their advertising policy of which you approve, but they sharply contest FDA's position of authority to regulate and so forth.

Dr. McCLEERY. Right. I did not feel compelled, knowing that Merck would testify tomorrow, to say they disagreed, feeling they would probably get around to that themselves tomorrow.

Senator NELSON. All right. I think the two fit together.

Dr. McCLEERY. Thank you.

Soon after this episode, Merck began to show significant improvements in its advertising practices for prescription drugs but not before it ran, I would say inadvertently, because it is hard to stop a hard-running advertising campaign—in the November 1966 issue of the American Journal of Medicine, another ad which contained most of the faults of the original July ad, plus some additional new faults.

I will expand on this.

It represents a very serious kind of advertising practice that I would like for you to understand, and to be aware of what kind of bases we are criticizing ads on, for your own purposes.

You have heard me refer to the articles used in the July JAMA ad, by two Englishmen, Hart and Boardman in the 1963 issue of the British Medical Journal. While the authors had in fact published the

report quoted in the Merck ad, we felt that Merck had no right to adopt the quotation in their 1966 advertising. The quotation from an article by Hart and Boardman in the BMJ, October 18, 1963, was used under the ad's caption "Rheumatoid Arthritis," and the quote that the company chose and chose to adopt as their own, was "The first noncorticosteroid agent which produced a predictable and measurable reduction in joint swelling in most cases of active rheumatoid arthritis."

Senator NELSON. That is a quote from the British Medical Journal from an article by Hart and Boardman.

Dr. McCLEERY. Yes, sir. Our comments with reference to this 1963 quotation are that, first, it does not represent a true statement of the effectiveness of the advertised product, Indocin. And in this regard, the company, we feel, is responsible for choosing and using an author's view; that it becomes in this effect their own, that they are responsible.

Senator NELSON. What you are saying is that they quoted Hart and Boardman accurately, but Hart and Boardman were incorrect?

Dr. McCLEERY. I do not think I will get around to my view on that if I can avoid it. I am saying that they quoted the article correctly. Whether it represented a correct view of the drug, other than in the mind of the authors, is a responsibility, I say, that the company has to assume—that when they choose a view expressed by an author in the scientific literature, that they have to stand on whether or not that represents a general view that is accepted widely by the medical profession at the time that they use it in an ad—that they must assume responsibility for making that view their own view.

Senator NELSON. All right.

Dr. McCLEERY. Now, the approved package insert for the product does not contain the promissory concept represented by "most cases" or "predictable," which were the views of Hart and Boardman.

Senator NELSON. Will you explain that. You are referring back to the quote from Hart and Boardman?

Dr. McCLEERY. Yes, sir; all of this will be in reference to that one quote—all that follows.

Senator NELSON. And you are saying that—

Dr. McCLEERY. That the approved package insert reflecting the agreed-upon view of the drug between the Government and the company does not contain the concepts of the features of the drug expressed by Hart and Boardman in their view—that the company thereby chose an opinion of someone else which was not, and has not, been approved for representing the drug in the package insert.

Senator NELSON. Are you saying that if the company requested to use the words "most cases," and "predictable" in the package insert, you would not have approved that language in the product package insert as of that date?

Dr. McCLEERY. That is not my responsibility, nor do I have enough information to make that judgment. I am saying that the package insert of record at the time the ad was printed did not contain these concepts, these promises. The companies are obligated in our view by the law, and the regulations written on it, to describe a drug, their drug, not beyond the terms included and approved in the official labeling for the drug. This is a baseline for the judgment of advertising,

and it is a baseline we are trying to establish in the mind of the industry. It should be their benchmark in keeping their claims within the approved concepts concerning the nature and effectiveness of the drug. It is the official document, negotiated for all drugs of this type, the so-called package insert.

Senator NELSON. Do I understand you correctly that they may use words in ads that are not in the package insert, but they may not make claims for the drug's performance that extend beyond the authorized claims that they are able to make in the package insert?

Dr. McCLEERY. Right; we are saying if this kind of information appears in the scientific literature, or as a result of research, the company has a very good legal method to begin to use this in advertising. They should gather together this kind of information and submit it to the Food and Drug Administration as a supplement to their New Drug Application, have this evidence judged and agreed on between the manufacturer and the agency, and get it into the package insert, and then they may indeed use it in their advertising. But the way not to do it is through the route of advertising.

Senator NELSON. If this is correct, what you are saying is that you have the legal authority to prohibit them from putting in an ad a claim for the drug that extends beyond the approved claims made for it in the package insert?

Dr. McCLEERY. Yes, sir. I believe that is true.

Senator NELSON. I am not familiar with your authority on that. Is there any question about the law on that?

Dr. McCLEERY. May I ask you to ask Mr. Goodrich?

Mr. GOODRICH. No, no question on that, Senator.

Senator NELSON. What are the penalties for violation of the law on that point?

Mr. GOODRICH. The same penalties for shipping any other misbranded drug, which is a maximum of a thousand dollars, and in the case of an individual up to a year in jail. But the regulations, the authority to specify what should be in the ad, is granted to us by the Kefauver-Harris amendments, and our regulations provide, acquiesced in by the industry, that in advertising drugs that had been cleared through the new drug procedures, the only permissible claims were those that had been approved.

Here the point is that the claim that this product is effective in most cases and gives predictable results were not approved. We went over yesterday, in connection with Dr. Hodges' statement, the points made at the time of approval, in which the limits of the claims were spelled out. The record yesterday will show that the breadth of this claim was not permitted.

Senator NELSON. Well, I would assume that anybody reading the package insert, and reading the ad could easily see that the ad is making a claim beyond what is authorized in the package insert.

Mr. GOODRICH. We think so. That is the simplicity of our regulatory scheme—to have the approved label as an identifiable, usable benchmark for all promotional efforts—advertising or direct mailing.

Senator NELSON. Do you have the authority to require that an ad be submitted for approval in advance of publication?

Mr. GOODRICH. In extraordinary circumstances, yes.

Senator NELSON. What are those circumstances?

Mr. GOODRICH. Where the product has a possibility of serious adverse effects or of causing fatalities. This was one of the issues that was in dispute when the Kefauver-Harris drug amendments were passed. There was a strong feeling on the part of the industry that we should not have routine preclearance. Of course we did not want that. But we said it would be necessary in some circumstances to have advance preclearance. As the regulations worked out, a provision was inserted to require preclearance when a newly discovered serious hazard or fatality came about, and we have a mechanism through which the company itself, on being notified by us of this new hazard and requirement of preclearance, can submit a program for their advertising that will assure prompt transmission of this important information to the profession through the company's promotional efforts.

Senator NELSON. You referred to a new drug?

Mr. GOODRICH. Any prescription drug, Senator, whether it be a new drug, or certified antibiotic, or even a prescription drug that has been on the market for a long time, and is under the grandfather protection for effectiveness. If we should learn that even an old drug suddenly had been discovered as a causative factor in serious adverse experience or fatalities, we have the authority to require preclearance of ads and to make sure the profession is notified through all mechanisms of this new hazard.

Senator NELSON. Supposing it is a new or an old drug and it is on the market; it is a very toxic drug, has dramatic side effects, such as this one or chloramphenicol, or any one of many, many more, and the company continues to put in its advertisements, such as this one, claims that extend beyond what is authorized in the package insert—do you have the authority, when that happens, to say, "From now on we will insist on preapproval of the ad"?

Mr. GOODRICH. Yes.

Senator NELSON. Have you ever exercised that authority?

Mr. GOODRICH. We have not. In this case, as Dr. McCleery's statement shows, we met with the firm on November 11, 1966, which was less than a month after we challenged this ad, this promotional practice, publicly, and the firm immediately developed a program to change its advertising practice. It was not necessary for us to require a preclearance. We have the authority to do so.

Senator NELSON. If I understand your testimony and other previous testimony before the committee, there have been a number of cases where the advertising for a drug has made a claim beyond the claims approved for the package insert; is that correct?

Mr. GOODRICH. Yes. And our reaction to those ads has been prompt and decisive in calling the company in, Dr. Goddard himself meeting with the companies to go over the defects, and to make sure that the company does and will immediately communicate with the profession to call attention to these defects. There have been, I believe, 21 or 22 letters in the last year and a half involving these advertising practices. We will put those into the record for you, so that you can see both the details of the advertising abuses that called for the letters, and the mechanisms that we used to require the companies to communicate this information to the profession.

SENATOR NELSON. What puzzles me a little bit is that this has been the law since 1963, has it not?

Mr. GOODRICH. The law was passed in 1963. It required that before we could do anything on advertising, we had to promulgate the regulations. We set to work promptly at that. We promulgated the regulations effective in 1964—after confrontation with the industry. The regulations became effective at that time. The original enforcement actions were—some were taken, but it was not until Dr. Goddard became Commissioner that this program was sharply stepped up, and I believe since certainly March of 1966—he came in February or March—I forget which—but soon after he came, it became one of his most—one of his highest priority programs. It has been a high-priority program since.

Senator NELSON. So the regulations were promulgated about 4 years ago.

Mr. GOODRICH. Yes, sir. As a matter of fact, we now have under consideration—we have had over about the past year—an improvement in those regulations in terms of making them much more specific. This improvement will be carried out very shortly. But meanwhile, we think the regulations are entirely adequate to deal with the major problems of advertising. We are revising them simply to be more specific and to avoid any contention on the part of the pharmaceutical industry that they did not understand what was required, or what our attitude towards specific kinds of advertising practices were.

Senator NELSON. Have there been any cases where the penalties under the law were levied against any of the companies?

Mr. GOODRICH. Yes. There has been one prosecution involving a product called Pree MT. There have been a number of others under discussion back and forth with the Department of Justice. Several of them are in controversy.

Senator NELSON. Do I understand you to say the penalty is a thousands dollars?

Mr. GOODRICH. Yes, sir—for each shipment of the drug. So there is a possibility of a substantial penalty.

Senator NELSON. We are talking about advertising in a journal now.

Mr. GOODRICH. Yes. But the offense is in terms of an interstate shipment of a supply of the drug.

Senator NELSON. The liability under the law is what?

Mr. GOODRICH. The introduction into interstate commerce of a misbranded drug, and the drug is misbranded because its advertising failed to comply with the regulations.

Senator NELSON. And what is the effective date from which you start measuring the penalty—the date of the publication of the ad?

Mr. GOODRICH. Yes—the ad must be related to a shipment made after the date the ad appeared.

Senator NELSON. And then the penalty is based upon the number of shipments, not the quantity?

Mr. GOODRICH. Yes, sir.

Senator NELSON. So if an ad were run on April 1 that violated the regulation by making claims that were not approved in the package insert, and one shipment of drugs was made after that, the maximum penalty would be a thousand dollars, is that correct?

Mr. GOODRICH. Yes, sir. Regardless of the size.

Senator NELSON. Do I understand you to say that in the last year and a half there have been 22 "Dear Doctor" letters sent out?

Mr. GOODRICH. I do not have the exact count. That is very close to it. We will supply the exact count.

Dr. McCLEERY. There have been I think 21 in just a little over 12 months.

Mr. GOODRICH. Right.

Senator NELSON. Were all these "Dear Doctor" letters based upon violations of what we are talking about here, a claim in an ad in excess of what was approved for the package insert?

Mr. GOODRICH. Not all of them. Most of them were, but there were a few instances in which the promotion in Physicians' Desk Reference was not up to date and current. I believe there were about four or five in that category. And the rest of them were concerned with journal advertising.

Senator NELSON. It seems to me from the cases I have seen, like the one today—would appear fairly clear violations of that—they clearly made claims beyond what was authorized in the package insert. How do you expect them to really conform if you are not tough about it?

Mr. GOODRICH. Well, I would rather—if you will permit me—not discuss the case that is going on.

Senator NELSON. I do not refer to any particular case.

Mr. GOODRICH. We feel we have been, and Dr. Goddard feels, I am sure, we have been quite strict with them in requiring the mailing out these "Dear Doctor" letters.

Senator NELSON. That is after the fact.

Mr. GOODRICH. And it is the only way that we can effectively correct that false message. The ad, after the fact, requires a communication to the profession, to make sure that it is understood that FDA regards the ad as misleading, and has requested the company to communicate with the profession, to tell what is wrong with the ad. This has been the pattern of the "Dear Doctor" letters. We think as of now it has been an effective mechanism for communicating with the profession about proper advertising, and we hope that it has brought about improvement, industry wide, in terms of the quality of the advertising messages.

Senator NELSON. Well, as to the question of its effectiveness, you were here yesterday at the hearing when we discussed the "Dear Doctor" letter that was sent out by Merck and which ended up being a promotional plug for the drug. The FDA subsequently had to get them to send another "Dear Doctor" letter to supplement the first one. But, in the second one you did not require that they say this is being sent because the first one was misleading.

Mr. GOODRICH. The first one was sent without our approval, and the second one did not refer to the fact that Food and Drug had required it. It was stated to you, and I can assure you it is true, that a great many "Dear Doctor" letters have been sent since that time, and they have uniformly referred to the fact that the Food and Drug Administration requested that they be mailed. Just the point you made yesterday—which we ourselves recognized early in this—the importance of including in the message the statement that this was an action precipitated by Food and Drug. There was of course much argument about that at all stages. But it has been a uniform requirement, I am sure, for a year now.

Senator NELSON. But you would agree, would you not, that one of these long closely typed "Dear Doctor" letters coming to a busy doctor is a whole lot less effective than a series of Roentgrams demonstrating how effectively this drug cures the patient's problem? So you end up with an after-the-fact situation where the doctor has been misled by the ad, and then you require that a letter be sent afterward which probably is not going to be read. As a matter of fact, since I have been conducting these hearings, many doctors, and good ones, have told me that the first thing they do with any of this material is throw it in the waste basket—they do not have time to read it all.

Mr. GOODRICH. We have, as you know, made sure these "Dear Doctor" letters are sent first-class mail, that they are sent in a distinctive type of envelope—the letters themselves, I am sure you will read them, are devised to put across the essence of the complaint about the advertising, and the details are put on the next page. We think those letters are effective as a means of communication.

Senator NELSON. They are not effective with the doctors who tell me they do not read them, any more than they are with the doctors who tell me they do not read the package insert.

If you are really going to make this work, why don't you do a couple of more things. One of them is, when they violate our regulations in an ad—this is a nice, beautiful, big color ad that I have here—why don't you just tell them you are going to send the "Dear Doctor" letter, and you are going to enclose a copy of the ad, because this is the ad that has been impressing the doctors; and, in addition, you are going to have the firm say "We have been required to correct this ad. This ad is inaccurate, and here is why."

No. 2—if you are really going to be effective, why don't you just tell the firm, "we are going to review for the next year all of your ads." I think they would shape up pretty fast. But if all you have is a little thousand dollars penalty here and there, and a little discussion here and there, you will have 22 "Dear Doctor" letters in the next 6 months, and have another 22 in the following 6 months. In the meantime doctors are being misled in a very important matter involving the health of their patients. And you have the power to do this. I do not know why you do not say, "You clearly violated advertising regulations, and for 1 year you must submit to us all ad copy in advance of publication." I think you would find that you would not have to send many "Dear Doctor" letters after that. They would take the package insert and use it as a basis for their ads.

Mr. GOODRICH. I think it is equally effective for the Commissioner to have the president of the firm come in and go over the faults in the ads, what was wrong with them, and then to require the company to mail out a first-class mailing to every physician in the United States, telling what was wrong with the ad.

Now, this is the mechanism that has been adopted. We think it is effective. We have seen in the case of Merck Sharp & Dohme, that after the meeting between the Commissioner and the president of that firm there was a significant improvement. We have seen this same pattern with most of the other companies that have been involved in "Dear Doctor" letters. But there have been some that have had more than one "Dear Doctor" letter. We are constantly working on this. Dr. McCleery has a relatively small staff. But I am sure Dr. Ley will agree this is a

top priority item in the Bureau of Medicine. We understand its importance in having drugs prescribed. As Dr. Jennings testified yesterday, the promotion of this drug was in part responsible for its tremendous use. It was launched with a message with which we cannot agree. So we adopted in March or June of 1966, a program of monitoring the initial promotion for every new drug approved to make sure the drug was launched on the right foot, and promoted to the profession for the conditions for which we had actually approved it.

Senator NELSON. Are you saying that you preexamine the advertising for all new drugs?

Mr. GOODRICH. We require them to submit, as soon as the first promotion is run—we do not require it to be submitted before it is run—submit that to us. Dr. McCleery's office processes that. If it is not in accordance with the conditions for which the drug has been approved, we then take action to be sure that it is.

Now, trying to preclear the ads at what you call the viewing board stage—this is just not a practical thing that we have felt we could do so far. We are calling for the ads to be submitted as soon as they are first placed. We are exercising care to make sure they are promptly reviewed.

Senator NELSON. Well, I do not know what the problem would be in preclearing all ads. I assume it would be massive. I am not talking about that. An ordinary layman such as myself can look at the ad promoting Indocin for gout, and knowing what I do about it, see the misleading point there, when they use the phrase "drug of choice." I know why they did it. I know why their highly paid advertising experts sat all day long figuring out the best phrase they could use to convince the doctors to prescribe their product.

The company knows that. So I do not know why you should not say to the company, "This is an overt, gross violation, and you know it, and you are the one company that is going to spend the next year submitting your ads for preclearance from us." I think if you did that once or twice, you would end up with very, very few "Dear Doctor" letters, and then you would not be permitting the misleading of the medical profession by ads such as this one.

My question is, Why don't you really get tough with these firms?

Mr. GOODRICH. I think we have been as tough as possible within the limits of our people. This is a good suggestion. But if spending time to preclear all the advertising—

Senator NELSON. Just a minute. I have never said that. I have suggested that you notify the industry that in clear cases of ads where the claims for a drug go beyond the package insert, the FDA will preclear the ads of this particular firm for the next 6 months or the next year. Then you are not going to have very many violations to bother with; that is my point. And if you told them also that they are going to have to send the ad to all doctors and tell the medical profession in the "Dear Doctor" letter, "We misled you in that ad; we made claims not permitted in the package insert and the FDA has told us to send you this ad and correct the ad," in my judgment you would not have much problem with this any more. The medical profession would no longer be subjected to misleading ads of the sort that caused Dr. Goddard to say of chloramphenicol, "I am at my wits end as to how to effectively warn the profession." I know why. Because the industry

runs ads like this. If I were a practitioner out in the country someplace, with a patient, and saw an ad like this showing feet and hips and hands, and stating that Indocin "extends the margin of safety," I would be impressed, too. After all, this is the Journal of the AMA—I am shocked that they would even run it. But here it is. I am a doctor. And I have high respect for the JAMA. They would not permit cheating in their advertising—I know that. And this distinguished company would not try to mislead me. So I prescribe it. And that is why the testimony was yesterday that this drug is being widely misused.

All I am saying is, for heaven's sakes why don't you do something instead of all this fluff-fluff we get all the time that goes on and on. It is a simple answer. You have the authority. Tell them to stop it "or we are going to review all your ads." And I predict you will be able to come back in 6 months and say "Senator, we have no trouble with advertising any more."

Mr. GOODRICH. Our answer is on that that we did tell Merck Sharp & Dohme, quite bluntly and quite pointedly, that the ad was bad, they stopped running it within 2 weeks after we told them, they destroyed, according to their statement, \$73,000 worth of comparable promotional material. They have been, according to the statement from Dr. McCleery made here, better since that experience. And he has in fact been over some ads with them to—brand new products, to show that we did get the messages across to this company. We think we have gotten it across to others. But your suggestion is a good suggestion, and we will certainly consider it.

Senator NELSON. Well, if I am around here for that long, the next time I find an ad that extends the claims beyond what is allowed in the package insert, I am going to invite you back, and we will talk about it again, and find out whether you are still satisfied with the methods you are using. I am not saying you have not improved them a lot.

Mr. GOODRICH. And I am not saying that the present method, Senator, is a hundred percent or the best one available. But it was one that was within our capability, it was one that has been carried out, I believe, with effectiveness.

Senator NELSON. Well, as you say, I think Dr. Goddard has done a magnificent job. I just think it is nonsense to permit this to go on, and you have been pretty soft on the industry. They know what they are doing. They are fooling the public—particularly the doctors. And it ought to stop. A great industry like this should not be overpromoting drugs for nonindicated cases. It is as simple as all that. Now, as long as they can get by with it, and make money, I guess this is what happens. I am not saying that it is a criminal offense. We had the same thing with the auto industry. As long as they could give us cheap tires that would not even hold the car, they did so. But, then we passed a law telling them to stop it. That does not mean the automobile industry is not a great industry—it is. But putting on cheap tires saved them \$400 or \$500 million a year, so they did it. And, it took Congress to do something about it. And the industry, or if necessary, the Congress ought to do something about this, because it has gone too far.

Mr. GOODRICH. We think Congress did do something about it. And in dealing with patients taking drugs, we expect a higher responsibility even than the automobile manufacturers.

Senator NELSON. Well, I think if you told those who drafted the Kefauver-Harris law, passed in 1963, that we would still have this kind of advertising going on in 1968, they would tell you that the will of Congress has not quite been complied with. Correction of such ought to happen sooner than 5 or 6 years.

Mr. GOODRICH. And I would agree with them.

Senator NELSON. We will take a 5-minute recess at this time.

(At this point in the hearing a short recess was taken.)

Senator NELSON. Let us resume, gentlemen.

Doctor, the minority counsel has a couple of questions.

Mr. GROSSMAN. Mr. Goodrich, I want to get a clear idea of this preclearance authority which you presently have—I think we just sort of skimmed over the fact that you do have some preclearance authority. Where and when does it apply, and when have you used it?

Mr. GOODRICH. It applies in the language that Congress adopted—except in extraordinary circumstances there shall be no requirement of preclearance of ads—section 502(n), Federal Food, Drug, and Cosmetic Act.

The implementing regulations say that when the Department learns of a newly discovered serious hazard that has not been widely disseminated, not widely known to the medical profession, it can require the preclearance of ads. It specifies there that upon being notified of the necessity for preclearance, the company can develop a plan, develop and present a plan to us which will assure that promptly their ads will cover this new hazard in which case preclearance would not be required.

There have been no instances so far in which preclearance has been required.

Mr. GROSSMAN. Required.

Mr. GOODRICH. Under those regulations.

Mr. GROSSMAN. That there have been no instances?

Mr. GOODRICH. Right.

Mr. GROSSMAN. You have never sought to implement this, because you never thought there was anything serious enough. Is that what we are to interpret?

Mr. GOODRICH. Haven't thought there was anything in terms of fatalities or serious side effects that was not promptly reflected in the ads.

Mr. GROSSMAN. Now—

Mr. GOODRICH. We have not run on to such a case.

Mr. GROSSMAN. How many deaths do you need before something becomes serious enough? What is your criterion here? I do not understand when you are going to use the preclearance authority.

Mr. GOODRICH. We are going to use it when a newly developed, newly discovered hazard is learned by us, and the company fails to immediately provide for including this information in its promotional program. Our experience has been that this newly discovered information is processed through our supplementary review, and is promptly put into the promotion.

Mr. GROSSMAN. What I am trying to say is—you talked about reacting to this, having meetings with companies about actions that they have taken, following up—everything is reacting or following up. I want to know, in other words, in what circumstances you feel you should act, and not react.

Mr. GOODRICH. Well, I think we have been doing most of the acting to initiate these meetings. I am sure we have.

Mr. GROSSMAN. I think that the companies have done some things that have forced you to react to them. What—I am trying to say—in other words, as far as we are concerned, this section 502(n) is really worthless—it has never been used, and you do not think there have ever been indications that the—

Mr. GOODRICH. I do not think that is so at all. This preclearance proviso in the section, which Congress told us not to routinely pre-clear ads—

Mr. GROSSMAN. I did not say you should routinely preclear. In other words, there is authority for you here to use preclearance, as I understand it, in hazardous situations. Now, I want to know what you consider hazardous. Obviously this was not a hazardous situation. Chloramphenicol—has there been anything you can think of that might be hazardous? In other words, how many deaths do you require?

Mr. GOODRICH. This was a serious situation, and we did get the company in within 2 weeks after the ad, and required the "Dear Doctor" letter shortly thereafter.

Mr. GROSSMAN. Do you require preclearance on all their advertising now?

Mr. GOODRICH. No. But they have been over—after we first had our discussion about this, their lawyer and their physician in this area came down to Washington, and went over a series of their ads with us, to make sure that they did fully understand what we intended, and their performance and behavior since that time has been improved.

Mr. GROSSMAN. Dr. McCleery, do you have anyone in your division who is assigned to decide when a drug is hazardous, and should become part of the section 502(n) proceedings?

Dr. McCLEERY. No, I have no one specifically assigned. The information of the kind that you are talking about would be developed principally in the area of the Office of Marketed Drugs. If they, in their work in surveillance of the reports of new adverse reactions of drugs on the market, would find an instance of this kind that they felt was not generally known—that the profession had not been prominently and widely informed, then at that point we would be able to enter in and to act as agents of this particular requirement of the law. We would not develop the information.

Mr. GROSSMAN. Is it fair to say that the committee could interpret that since 1964, since section 502(n) went into effect, there have been no cases of hazardous drugs which would qualify for preclearance? There have not been any?

Dr. McCLEERY. The paragraph in the regulations which give form to this section of the law that Mr. Goodrich talks about, is paragraph 1.105(j), and we have not as an agency invoked the provisions of that paragraph of the regulations.

We have, on the other hand, precleared many ads.

Mr. GROSSMAN. I am just thinking back to what Mr. Goodrich was discussing before—there are a lot of questions on which Congress has gone far enough. I just wonder whether 502(n) does not give us authority; and whether authority that you have could be used and has not been used.

In other words, it is one thing to say that the Congress should legislate. But when it has legislated, and there is a broad discretion that has not been enforced, it is not our job.

Dr. McCLEERY. I do not think I could agree with you that it has not been enforced.

Mr. GROSSMAN. Section 502(n).

Dr. McCLEERY. 502(n) is the broad language, and includes as one of its parts the exclusion that except in extraordinary circumstances we should not require a company to preclear its ads, as a part of that section of the Kefauver-Harris amendment.

Mr. GROSSMAN. I will not pursue this.

I wonder if you can answer as to when you think an extraordinary situation exists?

Dr. McCLEERY. I believe that paragraph 1.105(j) is the paragraph of detail in the regulations which gives form to one view of "extraordinary circumstances." In the negotiations with the industry in 1963, at the time the regulations were being proposed to the industry, this was a prominent feature of difficulty in the industry's acceptance of the original regulations written on the basis of the amendment to the act. That the paragraph exists at all, I think, has had an effect which has been salutary in causing companies to be aware of the need to move more quickly, than they might otherwise, to get new warnings into advertising.

Mr. GROSSMAN. I would question whether they would act because of their fear of your implementation of it. We have not seen very many examples of it.

Senator NELSON. Mr. Goodrich, so that I have this clear in my own mind—we have referred several times to your authority to preclear ad copy and I think, in that context, you have always referred to new drugs.

Mr. GOODRICH. If so, I misspoke myself. The advertising provisions apply to all prescriptions.

Senator NELSON. That was my impression. So if a drug is on the market, no matter how long it has been there, and the company at some stage makes claims that extend beyond the authorized package insert claims, you do have authority in that case to preclear a future ad or ads.

Mr. GOODRICH. Yes—and even with drugs on which we have no approved package insert—that is the drugs on the market since 1938, without new drug clearance. If there should be discovered some new hazard about such a drug, it would be possible to preclear, and to require preclearance of the ad. Only, I believe, 2 years ago we reclassified a drug on the market in 1936 as a new drug, because of a newly discovered hazard in it, and did take regulatory action. It was not advertised broadly, so it was not necessary to preclear advertising. But we did require its reclearance through the new drug procedure. It was a product called Dipyrone, discovered to have some blood hazards.

Senator NELSON. You referred to drugs marketed before 1938. Do you approve a package insert from them?

Mr. GOODRICH. No; they are totally exempt from preclearance. They are required to have a package insert with full disclosure information in it. But we do no preclear it.

Senator NELSON. You do not preclear the package insert?

Mr. GOODRICH. We do not. The law exempted—just drew a line—products on the market June 1938 and before. So long as they have the same claim they are not subject to new drug preclearance.

Senator NELSON. Have the same what?

Mr. GOODRICH. Same claims in use as in 1938.

Senator NELSON. Supposing you found out that these claims were not justified. Do you have any authority to require that changes be made?

Mr. GOODRICH. Yes. We would have the authority to proceed through the courts to charge them to be—as being misbranded, and then for us to bear the burden of proving the claims false rather than the burden under the new drug provisions being on the company to prove the drug's effectiveness. That is just a difference in the burden there.

Senator NELSON. Do you know what percentage of the prescription drugs in the marketplace are exempt from your authority to regulate?

Mr. GOODRICH. No; we do not have any reliable figures on that. We are pretty sure that a great majority of the drugs now in use are drugs that have entered the market since the enactment of the new drug law in 1938. There would be a number of oldtimers, of course, that were on the market in 1938, that are still around—phenobarbital, thyroid, a lot of others. But the great majority of drugs, I think I am correct in saying, now in use are drugs that have been developed between 1938 and the present time. This is why we regard as quite important, our contract arrangement with the National Academy of Sciences, to review the claims of effectiveness for these drugs marketed between 1938 and 1962, enabling us to bring to bear the new requirements of effectiveness on those products. Congress' solution to this in 1962, rather than exempting all those premarketed drugs completely, was to give us the right to, through administrative action—to go back and review the claims, product by product, and to be sure that they were effective as claimed.

Senator NELSON. That authority extends just on drugs marketed from 1938 to 1962?

Mr. GOODRICH. Yes, sir.

Senator NELSON. And you are in the process of reviewing them now?

Mr. GOODRICH. Yes, sir. The contract has been virtually completed, I think. We are getting the reports now, and we have begun to implement the reports by requiring changes in the labeling and packaging.

Senator NELSON. Once the review has been done, do you then, under the law, have the authority to control the package insert?

Mr. GOODRICH. Yes, sir. But we have a dispute with the drug industry about the extent of our authority. But we think we have enough authority to carry this forward.

Senator NELSON. Go ahead, Doctor.

Where were you?

Dr. McCLEERY. I would like to pick up in the middle of page 8, paragraph c.

We believe that the quotation that we have been talking about misleads in that it is obsolete when used in the ad in 1966, in that it fails to take into account more recent, more scientific, but less salubrious opinions of the same authors available to the firm in medical literature published about a year prior to the ad. The company was aware of the more recent literature, and the facts are that—(1) in 1965 the

same authors published the results of a much better controlled and double-blind study on a larger population than the 1963 paper—here 26 patients crossed over on both indomethacin, and the competitive product, phenylbutazone.

(2) This was a study of the response to the marketed capsules within the limits of approved dosage, the authors ended the paper with a note of thanks to company personnel “for generous supplies of indomethacin,” it was published in the same journal as the first article (British Medical Journal, 2: 1281, Nov. 27, 1965), and was available well before the ad was created and published.

(3) The overall patient response greatly favored the competitive product to an extent that was statistically highly significant, for example, when the 2-month blind trial was over “\* \* \* 15 patients preferred phenylbutazone, 10 found them to be equally effective, and one preferred indomethacin.”

(4) The authors’ conclusions re Indocin were strikingly different (the key words “predictable” and “in most cases” no longer were included) after this study, that is, “\* \* \* the first nonsteroid to produce a measurable reduction in joint size in selected cases of active rheumatoid arthritis.”

Now, the phrase “the first nonsteroid” is common to both articles. It should be noted that the authors’ retention and the company’s use of the phrase “the first” is in my view highly questionable.

Within the authors’ own results in the 1965 article, they included the observation that reduction in joint size occurred not only in patients on indomethacin, but also on phenylbutazone as well, and that taking into account both the number of patients improved, and the extent of reduction, differences between the two drugs were not statistically significant. And yet the authors were still using the phrase “the first nonsteroid,” and so on.

It is difficult for me to see any validity or significance to the claim “the first” especially when the authors failed to find such difference in the reduction that they did find—to find any statistically significant difference between the amount of reduction.

Mr. Chairman, since your committee may wish to consider the Hart and Boardman papers in some detail, I have made copies of both papers available to you and for the record, and I have gone into some detail on this point, because it typifies several advertising practices which we regard as seriously misleading.

Senator NELSON. We will print those in the record. If I understand you correctly, what you have said is that the company quoted from an early study by these two doctors.

Dr. McCLEERY. That study being of less quality than the later.

Senator NELSON. And was the second study which modified the position taken in the first study published and available at the time they ran the questionable ad?

Dr. McCLEERY. Yes, and known to the company long before that, because they were in contact with the authors of the study and supplied the drug to the authors, so that they were well aware of the study going on.

Senator NELSON. So here you say there is a clear-cut case where they knew a subsequent study modified the original one; yet, they continued to use in their advertising a quote from the original study.

Dr. McCLEERY. Right. And which quote was not the opinion of the author at the time that the ad was created?

Senator NELSON. Yes.

Dr. McCLEERY. You might wonder, as we did, why the company might choose—if they chose, it may be a matter of inattention to the literature—but whether they chose to use the '63 paper and ignore the '65, I do not know. But I think I would like to offer you evidence from the second paper—just a few brief recounts of the results reported by the authors in the second paper which may suggest why the second paper was undesirable as a form of promotion. And I would like to read a few excerpts from the Hart and Boardman paper of 1965.

Senator NELSON. You say the company was aware of the second paper?

Dr. McCLEERY. I cannot say that. I can only assume that if they were not, that it was a matter of inattention which I would not find excusable.

Senator NELSON. Since it was a trial run on their own drug.

Dr. McCLEERY. And it was published in the same journal, and was in print available well before they created the ad, and since they were clearly aware of the research of Hart and Boardman, having been in contact with them from the days of the IND.

I would like to read some of the comparative results which this ad did not point to—which a doctor might see if he read the 1965 article.

The following from the article, not used by the company in its promotion, are some of the results found by the same authors.

As far as subjective signs are concerned, when they asked the patients at the end of the trial which one was found by the patients to be more satisfactory, "15 patients preferred phenylbutazone, 10 found them to be equally effective, and one preferred indomethacin. This difference is statistically significant with a 'p' value less than 0.001."

They go on at much greater length and deal with the question of pain as recorded by them for each patient during the month on each drug. And they found that the "improvement in pain"—that five on phenylbutazone, but only two on indomethacin found their pain relief better, and that 19 found no difference.

As far as "joint stiffness" was concerned, assuming a 25-percent difference to be significant, five were less stiff during phenylbutazone, and only one less stiff on indomethacin—20 patients found no detectable difference.

As far as the very commonly used parameter of judgment, "early morning stiffness," for drugs in this category, they found that in the first month on phenylbutazone seven patients were improved, and on indomethacin only three improved. In the second month, on indomethacin improvement occurred in three patients, and on phenylbutazone four improved.

As far as "grip strength" was concerned, I won't review the comments in detail, but there was no real difference between the two drugs on that parameter.

As far as the objective "change in joint size," which is a common feature of the 1966 ad, and is related to the authors' comment about the "first nonsteroid" to produce reduction in joint size, these are the actual figures given by the authors in their paper, which precede their conclusions. So they say—assuming a change of three ring sizes

in joint size to be significant, there was no difference in 17 patients, five were better on indomethacin, but also four were better on phenylbutazone. And they go on to conclude that this difference between the drugs' effect is not statistically significant. But it is significant that the number of patients showing reduction in their joint size was almost equal between the two drugs, and that there also was a positive effect for phenylbutazone noted in the same study that showed a positive effect on some cases with indomethacin.

Senator NELSON. That is from the second study.

Dr. McCLEERY. Yes, sir. Whether these results have any connection with its lack of desirability, or are related to the company's decision not to use it as a source of reference, I do not know. But those are the authors' conclusions in the second paper.

Now, there are several other claims made in the JAMA ad to which we objected in detail in our internal memos. For example, one of the most serious of all was this matter of a drug of choice, to which I referred. Whereas in the earlier ads the company did change these quotes to tone them down by inserting the bracketed letter "a," the last ad in the series, later, in November, quoted it unadorned, unchanged, as "the drug of choice."

I might say in passing also that the Hart and Boardman article used in regard to the treatment of gout, which is the most right block of the ad, was based entirely on the indomethacin formulation that was not marketed, the tablets. Furthermore, the dosages used by the authors, which gave the results that led to "the drug of choice" opinion, were far in excess of the upper approved safe limit when the drug was marketed in this country in capsule form. Outside of all these features I would have to agree that the use of the quote is proper.

Now, Congress has already recognized that it is dangerous to promote a new drug with inadequately based claims for greater safety and comparatively greater effectiveness than established competitive products. Safe promotion can be based only on adequate clinical data, and then only with a complete awareness that the limited experience with the new drug as it enters the market, accumulated during its investigational state, may change rapidly and significantly when the drug is released for general use by physicians at large. Also experience will dictate changes from time to time as you have seen in the testimony yesterday, and for as long as the drug is marketed, very possibly.

Indomethacin was recognized from the first as a drug with significant capacity for adverse effects. We believe its promotion over the first year of its approved marketing improperly presented the drug to the medical profession—both as to the range of its effectiveness and as to the margin of its safety.

Mr. Chairman, this emphasizes, for us at least, the need for our continued special attention to the advertising of newly released drugs as they enter the marketplace, as well as that for older prescription drugs, to help provide assurance—and, I might add, I would like to insert the word "help" for the record here as a qualifier, which we so often insist that our opponents in advertising use—so with your permission, and with some seriousness, may I request that you insert the word "help" after the word "to"—to help provide assurance that they are fairly presented to the medical profession under the approved conditions of marketing. Further it demonstrates a need for constant sur-

veillance, both by us and by the manufacturer, of clinical experience to keep advertising messages in step with the realities for safe and effective prescribing of new drugs as more experience is developed during their marketing history.

Thank you. I will be glad to answer any questions.

(The complete prepared statement and supplemental information submitted by Dr. McCleery follows:)

STATEMENT OF DR. ROBERT S. MCCLEERY, ACTING DIRECTOR, DIVISION OF MEDICAL ADVERTISING, BUREAU OF MEDICINE, FOOD AND DRUG ADMINISTRATION, U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Mr. Chairman, I appreciate this opportunity of appearing before you this morning to discuss our experience with the advertising of Indocin. For the sake of brevity, and with your permission, I will submit for the record a statement of my educational and professional background.

Shortly after Dr. Goddard became Commissioner of Food and Drugs, in early 1966, the Agency's interests in prescription drug advertising were sharply accentuated. It was felt that manufacturers had had time enough to adjust to new requirements concerning advertising. Dr. Goddard spoke to the presidents of pharmaceutical firms, to their medical directors and to their advertising agencies to note what we regarded as a continuation of advertising abuses that had been so largely responsible for the enactment in 1962 of the Kefauver-Harris Drug Amendments and the promulgation in 1964 of the first advertising regulations.

The Fountain Subcommittee, House Committee on Government Operations, had reviewed with the Commissioner our programs in this important area of our public responsibilities. In short, industry's attention was brought emphatically to promotion excesses in many ways.

In June 1966, the Director of Public Relations for Merck & Co., Mr. John E. Fletcher, wrote to Theodore O. Cron, our Assistant Commissioner for Education, enclosing a print of an article that was about to appear in the July 1966 issue of *Pageant* magazine.

The story featured Indocin as useful for "bursitis," "trick knee," "tennis elbow" and "a host of other less common disorders characterized by pain and swelling in and around the joints." The support for these claims was largely lay testimonials some of which, according to the article and the firm, were made available to the writers by the sponsor of the drug.

Mr. Fletcher said that the firm was in no way responsible for the article, that the authors had heard of stories about the drug from a variety of sources and wanted to do an article about it, and that the firm had simply responded to this inquiry from responsible science writers. Mr. Fletcher said the article was in no way promotional and wanted to so assure the Agency.

The drug, of course, had not been approved for use for the above-mentioned conditions for which it was claimed to be effective in the *Pageant* article. We knew also that a popular article of this sort is apt to create a demand for the drug by the patients who read it. My office, the Division of Medical Advertising in the Bureau of Medicine, was asked to review the article for possible violation of the law, and to review also the advertising of this drug in medical journals to determine if the drug was being promoted to the medical profession on the basis of unapproved claims.

Our concern was that if the firm would make these data on unauthorized uses available to a free-lance team of writers, it might not be scrupulous in its advertising to the medical profession.

Identical advertisements which appeared in the *Journal of the American Medical Association* issues of July 4, 1966 and August 15, 1966, were found to be featuring the theme that the drug "extends the margin of safety in the long-term management of arthritic disorders." At the same time, the Office of Marketed Drugs was negotiating with Merck for changes in the labeling to emphasize the newly recognized hazards that had emerged during the first year of clinical experience since original approval of the drug.

The *JAMA* ads in July 4 and August 15, 1966 issues were analyzed and found to be defective, in our opinion, in several respects. I will first mention generally the major defects of this ad and then will be more specific regarding the details of our objections to certain of the features of this and of a later ad which appeared in November 1966. The basic theme of greater long-term safety in the ads was not supported by the clinical experience. To the contrary, the longer

the drug had been on the market, the more serious adverse experience information was reported.

The ad quoted apparently-authoritative sources without the full impact of the limited experience contained in the actual articles. And it featured, for example, one reference which on checking proved to be only a 2-inch abstract of a 1964 speech. The ad quoted the author's opinion that ". . . results have been uniformly excellent or good in ankylosing spondylitis." The same abstract also included the author's view that, while "Excellent results have also been obtained in some cases of rheumatoid arthritis . . . there have been striking failures as well." It is, perhaps, not surprising that, while the advertiser included this author's favorable remark regarding his experience with spondylitis, the ad turned to another author for a more favorable quote concerning the possible value of the drug on rheumatoid arthritis.

It offered the drug for "arthritis disorders," rather than solely for the four conditions for which it had been approved.

It characterized the drug as non-steroid—which of course it is—but failed to disclose in this connection that it had some of the major side effects of the steroids, e.g., an ulcerogenic effect.

It claimed that the drug extended the margin of long-term safety, without any evidence to support the claim—it quoted from isolated pieces of literature—one an excerpt from a symposium sponsored by the company—to claim that the drug was the drug of choice in gout and osteoarthritis of the hip, neither of which claims had been approved.

It quoted from two leading English authorities to the effect that the drug was useful in most cases of rheumatoid arthritis, when these authors had used the tablet and not the marketed capsule, and when their actual opinion, known to Merck, was that the drug was useful in only selected cases of rheumatoid arthritis.

It featured the claim of one of the participants in a Merck-sponsored symposium that he had had 500 patients on the drug for three years, when Merck's own records would have told them this was not true.

And finally in the "Brief Summary" of information on side effects and contraindications some of the major warning information was left out—such as the fact that indomethacin itself had caused ulcers, and that the drug should not be administered to children.

This exemplifies what may be called the euphemistic style of revealing warning information. The ad's "Brief Summary" translated the package insert's warning, "INDOCIN itself may cause peptic ulceration . . ." into the area of causal doubt in this manner: "Ulceration of the stomach, duodenum, or small intestine have been reported . . ." Further, the package insert's directness, regarding administration of the drug to children, became the "Brief Summary's" statement that "Safety in pregnancy and pediatric age groups has not been established."

Deficiencies in the ad were publicly noted in a speech before the Pharmaceutical Advertising Club in New York on October 20, 1966, by our General Counsel, Mr. Goodrich.

The firm protested and shortly thereafter, on November 11, 1966, a sort of armistice day, the firm's principal officers met with Dr. Goddard and his staff to go over the problem.

The firm reported that it had immediately ordered the ad discontinued after the October meeting and was taking a close look at all of its promotional efforts. Later, its physician and counsel responsible in the area of advertising came down to go over some ads for other products with us.

Soon after this episode, Merck began to show significant improvements in its advertising practices for prescription drugs but not before it ran, in the November 1966 issue of the *American Journal of Medicine*, another ad which contained most of the faults of the original ad, plus some additional new faults.

I will expand on this. While the authors, in 1963, had published the report quoted, we felt that Merck had no right to adopt the quotation in their 1966 advertising.

The quotation from an article by Hart and Boardman (Hart, F.D. and Boardman, P.L.: *British Medical Journal*, 2:965, October 18, 1963) and used under the ad caption "rheumatoid arthritis," namely, ". . . the first non-corticosteroid agent which produced a predictable and measurable reduction in joint swelling in most cases of active rheumatoid arthritis."

Our comments in reference to the quotation are that it:

a. Does not represent a true statement of effectiveness of the advertised product, "Indocin."

(1) The approved package insert for the product does not contain the promissory concepts represented by "most cases" and "predictable." represented by the words "the first." That the firm had previous knowledge of

(2) The approved package insert provides no basis for the comparative claim represented by the words "the first." That the firm had previous knowledge of the impropriety of the claim is evidenced by that in an earlier, similarly-appearing ad the company more cautiously excluded this phrase from the quoted clause and substituted "a" for "the first."

b. Misleads by its use out of the article's context in such a way as to present an unfair and distorted view of the drug's identity, safety and effectiveness:

(1) The authors had not used the marketed "Indocin" capsules, but instead employed an experimental tableted formulation.

(2) The authors had only 15 pertinent patients from which the represented conclusion was drawn. The reader would have been forewarned, and not overly impressed, if he had known the generalization "in most cases" rested not on a large experience from which a generalization might not be misleading, but on only a favorable result in 8 out of 15 patients.

(3) An unknown and unspecified proportion of the above results were obtained by dosages well over the 200 mg. upper limit of approved dosage, e.g., 300 mg. per day. The physician reader could not know from the ad that he could not necessarily expect similar results by employing dosages approved as safe in the drug's package insert.

c. Misleads in that it is obsolete and fails to take into account more recent, more scientific, and less salubrious opinions of the same authors available to the firm in medical literature published about one year prior to the ad. The company was aware of the more recent literature and the facts are that:

(1) In 1965, the same authors published the results of a much better controlled and double-blind study on a larger population (26 patients crossed-over on both indomethacin and the competitive product, phenylbutazone).

(2) This was a study of the response to the marketed capsules within the limits of approved dosage, the authors ended the paper with a note of thanks to company personnel "for generous supplies of indomethacin," it was published in the same journal as the first article (*British Medical Journal*, 2: 1281, November 27, 1965), and was available well before the ad was created and published.

(3) The overall patient response greatly favored the competitive product to an extent that was statistically highly significant, e.g., when the two months blind trial was over ". . . 15 patients preferred phenylbutazone, 10 found them to be equally effective, and one preferred indomethacin."

(4) The authors' conclusions re Indocin were strikingly different (the key words "predictable" and "in most cases" no longer were included) after this study, i.e., ". . . the first non-steroid to produce a measurable reduction in joint size in selected cases of active rheumatoid arthritis."

(5) It should be noted that the authors' retention and the company's use of the phrase "the first" is highly questionable.

(a) Within the authors' results in the later article they included the observation that reduction in joint size occurred not only in patients on indomethacin, but on phenylbutazone as well, and that, taking into account both the number of patients improved and the measured extent of reduction, differences were not statistically significant.

Mr. Chairman, since your Committee may wish to consider the Hart and Boardman papers in some detail, I would like to make copies of both papers available for the record. I have gone into some detail on this point because it typifies several advertising practices which we regard as seriously misleading.

Congress already has recognized that it is dangerous to promote a new drug with inadequately-based claims for greater safety and comparatively greater effectiveness than established products. Safe promotion can be based only on adequate clinical data—and then only with a complete awareness that the limited experience with the new drug, accumulated during its investigational state, may change rapidly and significantly when the drug is released for general use by physicians. Also, experience will dictate changes from time-to-time as long as the drug is marketed.

Indomethacin was recognized from the first as a drug with a significant capacity for adverse effects. We believe its promotion over the first year of its approved marketing improperly presented the drug to the medical profession—both as to the range of its effectiveness and as to the margin of its safety.

Mr. Chairman, this emphasizes the need for our continued special attention to the advertising of newly-released drugs, as well as older drugs, to provide assurance that they are fairly presented to the medical profession under the approved conditions of marketing. Further it demonstrates a need for constant surveillance, by both the manufacturer and the FDA, of clinical experience, to keep advertising messages in step with the realities for safe and effective prescribing of new drugs as more experience is developed during their marketing history.

Thank you for your attention. I will gladly answer any questions you may have.

[From the Journal of the American Association, Vol. 197, No. 3, July 18, 1966]

## extends the margin of safety in long-term management of arthritic disorders

INDOCIN® (indomethacin)

INDOCIN® (indomethacin)



A nonsteroidal anti-inflammatory agent which produces a predictable and measurable reduction in joint swelling induced either by acute rheumatoid arthritis

or by chronic rheumatoid arthritis.

INDOCIN® (indomethacin) 25 mg. tablets, 50 mg. tablets

and provides a significant therapeutic advantage over other nonsteroidal anti-inflammatories.

INDOCIN® (indomethacin) 25 mg. tablets

**Indications:** Chronic and acute rheumatoid arthritis, ankylosing spondylitis, degenerative joint disease (osteoarthritis) of the hip, and gout.

**Contraindications:** Active peptic ulcer, gastritis, regional enteritis, or ulcerative colitis. Safety in pregnancy and in pediatric age groups has not yet been established.

**Precautions:** Ulceration of the stomach, duodenum, or small intestine has been reported and, in a few instances, severe bleeding with perforation and death. Gastrointestinal bleeding with no obvious ulcer formation has also been noted; INDOCIN should be discontinued if G.I. bleeding occurs. As a result of G.I. bleeding, some patients may manifest anemia, and for this reason periodic

hemoglobin determinations are recommended. Use cautiously in patients with history of ulcer, gastritis, ulcerative colitis, and regional enteritis.

**Adverse Reactions:** Most common: headache, dizziness, lightheadedness, G.I. disturbances such as nausea, anorexia, vomiting, epigastric distress, abdominal pain, diarrhea. The C.N.S. effects are often transient and frequently disappear with continued treatment or reduced dosage; C.I. effects may be minimized by giving the drug with food or immediately after meals. The severity of these effects may occasionally require cessation of therapy. Infrequently observed side effects may include drowsiness, tinnitus, mental confusion, depression and other psychic disturbances,

# INDOCIN<sup>®</sup>

## INDOMETHACIN

a new, highly effective nonsteroid anti-inflammatory agent



Indocin<sup>®</sup> (Indomethacin) Dispersible  
Tablets (50 mg and 75 mg)

© 1973

**INDOMETHACIN** (indomethacin) is a nonsteroidal anti-inflammatory agent. It has been reported to have analgesic, antipyretic, and anti-inflammatory properties. It has been used in the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, bursitis, tendinitis, and gout. It has also been used in the treatment of acute and chronic musculoskeletal pain associated with muscle strain, sprain, and overuse. It has been used in the treatment of acute and chronic pain associated with headache, toothache, and dental procedures. It has been used in the treatment of acute and chronic pain associated with muscle strain, sprain, and overuse. It has been used in the treatment of acute and chronic pain associated with headache, toothache, and dental procedures.

Side effects include: dizziness, headache, tinnitus, pruritis, urticaria, angioneurotic edema, tight BUN elevation, usually transient, has been seen in patients, although the preponderance of evidence suggests that it does not adversely affect renal function, with the exception of those receiving it. Nevertheless, it should be used judiciously in patients with hypertension, as it has been seen in a few patients to cause an increase in blood pressure. At one phenothiazine and phenothiazine derivative, and may turn red and have symptoms such as nausea, vomiting, and diarrhea. If side effects develop, the drug should be discontinued. As with any new drug, patients should be

monitored closely for signs of toxicity.

**Warning:** Patients who experience

feelings of drowsiness on INDO-

CIN should discontinue the

drug immediately and seek

medical attention. The drug

should not be taken by

patients who are sensitive

to the drug. The drug

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One of the most promising antirheumatic agents that has been made available since the introduction of cortisone by Merck Sharp & Dohme.

[From the American Journal of Medicine, November 1966]

One of the most  
promising antirheumatic  
agents that has been  
made available since  
the introduction of  
cortisone by  
Merck Sharp & Dohme.

## extends the margin of safety in long-term management of arthritic disorders

### rheumatoid arthritis



The first non-corticotrophic agent which provides predictable and meaningful reduction in joint swelling in most cases of rheumatoid and ankylosing spondylitis.

INDOCIN® (Indomethacin) is a new drug in the non-steroidal anti-inflammatory class.

### ankylosing spondylitis



Therapeutic results have been uniformly good in ankylosing spondylitis.

Indocin® (Indomethacin) is a new drug in the non-steroidal anti-inflammatory class.

**Indications:** Chronic and acute rheumatoid arthritis, rheumatoid (ankylosing) spondylitis, degenerative joint disease (osteoarthritis) of the hip, and gout.

**Contraindications:** Active peptic ulcer, gastritis, regional enteritis, or ulcerative colitis. Safety in pregnancy has not been established. Not recommended for pediatric age groups.

**Warning:** Patients who experience dizziness, lightheadedness, or feelings of detachment on INDOCIN should be cautioned against operating motor vehicles, machinery, climbing ladders, etc. Use cautiously in patients with psychiatric disturbances, epilepsy, or parkinsonism.

**Precautions and Adverse Reactions:** Most commonly, headache, dizziness, lightheadedness, G.I. disturbances. The C.N.S. effects are often transient and frequently disappear with continued

treatment or reduced dosage. The severity of these effects may occasionally require cessation of therapy. G.I. effects may be minimized by giving the drug with food or with antacids or immediately after meals. Ulceration of the stomach, duodenum, small intestine has been reported and, in a few instances, severe bleeding with perforation and death. Gastrointestinal bleed with no obvious ulcer formation has also been noted; INDOCIN should be discontinued if G.I. bleeding occurs. As a result, G.I. bleeding, some patients may manifest anemia, and for this reason periodic hemoglobin determinations are recommended. Rare reports of effects not definitely known to be attributable to INDOCIN include bleeding from the sigmoid colon (either a diverticulum or without a known previous pathologic condition), perforation of preexisting sigmoid lesions (diverticul-

# INDOCIN<sup>®</sup>

## INDOMETHACIN

a new, highly effective nonsteroid anti-inflammatory agent

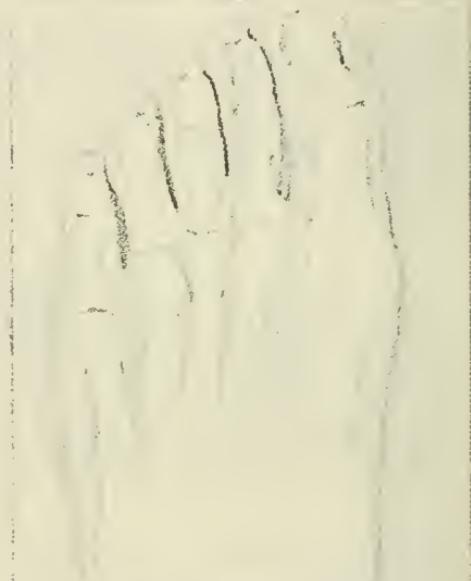


**Degenerative joint disease  
(osteoarthritis) of the hip**

**gout**

"...had some 500 patients on indomethacin for about three years. I find it an extremely good drug. I think there are certain areas where it will be. Without question the drug of choice in osteoarthritis of the hip."

George E. V. M. Nonsteroidal Anti-inflammatory Drug  
in Rheumatic Disease. New York: Pergamon Press,  
1969, p. 27.



**"Indomethacin is the drug of choice in acute gout"**

Hart E. D. and Goldfarb D. L. *Br. Med. J.* 2:283, Oct. 19, 1963

leucinoma), and hematuria. In other rare cases, a diagnosis of *psoriasis* has been made while the drug was being given. One patient developed ulcerative colitis, and another, regional ileitis, while receiving INDOCIN; when the drug was given to patients with preexisting ulcerative colitis, there was an increase in abdominal pain. Infrequently observed side effects may include drowsiness, tinnitus, mental confusion, depression and other psychic disturbances, blurred vision, stomatitis, pruritus, edema, and hypersensitivity reactions. Slight BUN elevation, usually transient, has been seen in some patients, although the preponderance of evidence indicates that INDOCIN does not adversely affect renal function, even in patients with preexisting renal disease. Nevertheless, renal function should be checked periodically in patients on long-term therapy. Leukopenia has been seen

in a few patients. Transient elevations in alkaline phosphatase, cephalin-cholesterol flocculation, and thymol turbidity tests have been observed in some patients and, rarely, elevations of SGOT values; the relationship of these changes to the drug, if any, has not been established. As with any new drug, patients should be followed carefully to detect unusual manifestations of drug sensitivity.

Before prescribing or administering, read product circular with package or available on request.

**MERCK SHARP & DOHME** Division of Merck & Co., Inc., West Point, Pa.

**where today's theory is tomorrow's therapy**

[From British Medical Journal, Oct. 19, 1963, pp. 965-970]

### INDOMETHACIN: A NEW NON-Steroid ANTI-INFLAMMATORY AGENT

(By F. Dudley Hart, M.D., F.R.C.P., and P. L. Boardman, M.B., M.R.C.P.)

The measurement of joint-swelling in the human subject is not easy, but in the assessment of drugs purporting to have an anti-inflammatory effect in conditions characterized by the presence of chronic inflammatory swelling, such as rheumatoid arthritis, some clinical measure is essential. We have found that the only practical and reliable measurement which can be done repeatedly and reasonably quickly in the wards is finger-swelling measured by jewellers' rings (Hart and Clark, 1951). All patients with active rheumatoid arthritis entering our wards have finger-swelling measured in this way twice weekly by the same clinician at approximately the same time of day as a routine measure. Also, the patient's own assessment of pain, stiffness, the number of analgesic tablets taken daily, the time taken to limber-up in the morning, and the clinician's assessment of grip strength, joint tenderness, and sedimentation rate are done routinely on all patients as measures of progress irrespective of the treatment given throughout their stay in hospital.

Measurable reduction of joint-swelling occurs regularly and demonstrably with steroid therapy, but not with salicylates, phenacetin, paracetamol, or the pyrazoles (phenylbutazone or oxyphenbutazone) as measured by this method; and since the early use of the corticosteroids and corticotrophin no other therapeutic substances of the many we have tried have produced a measurable reduction in swelling of the interphalangeal joints. It was therefore a pleasant surprise when we found that in indomethacin (MK 615) we had the first non-corticosteroid agent which produced a predictable and measurable reduction in joint-swelling in most cases of active rheumatoid arthritis.

### CHEMISTRY

Indomethacin is a non-steroid anti-inflammatory and antipyretic agent. Its activity does not depend upon pituitary-adrenal stimulation and it is fully active in adrenalectomized animals. Chemically it is 1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindol-3-acetic acid, having the empirical formula of  $C_{19}H_{16}NO_4C_1$  and a molecular weight of 357.8. It is relatively insoluble in water but soluble in the common organic solvents. It is rapidly cleared from the plasma, having a half-life of 0.3-4 hours in various species. From 46 to 63% of an intravenous dose of indomethacin-2-C<sup>14</sup> is rapidly excreted in bile of dogs, guinea-pigs, and monkeys (Hucker, Zachei, and Cox, 1963). Its anti-inflammatory activity can be demonstrated in rats by the cotton-pellet granuloma-inhibition test and by inhibiting oedema on subplantar injection of irritant agents. Granuloma inhibition can be observed by oral administration or by local application to the cotton pellet in the same animal. After oral administration to rats the drug appears to be well absorbed and gives an estimated plasma half-life of about 21 hours; about 90% of the drug in plasma is bound to the non-diffusible constituents. Excretion in rats is largely through the kidney, little being found in the faeces. That rat and the dog apparently tolerate the drug less well than does man or monkey.

Antipyretic activity has been demonstrated by inhibiting the fever produced by injection of *Escherichia coli* endotoxin in both rats and rabbits. Analgesic effects could not be demonstrated in mouse or rat by current methods. Toxic effects in rat, dog, and monkey consist largely of gastrointestinal irritation, monkeys tolerating larger doses of the drug than rat or dog. Judged by the work on animals, gastro-intestinal toxicity seemed to be the only effect likely to occur in man, but early clinical trials in the United States of America indicated that it was usually well tolerated by the human digestive tract (R. Hodgkinson, personal communication, 1963).

### MATERIAL AND METHOD

Indomethacin has been used in the treatment of a group of patients in whom a clinical response might be anticipated from administration of a compound with anti-inflammatory, antipyretic, and possible analgesic properties (see Table I).

TABLE I.—OVERALL CLINICAL RESPONSE IN 99 PATIENTS TREATED WITH INDOMETHACIN

Disease	Number of patients	Clinical improvement	No clinical improvement	Inconclusive
Gout.....	15	13	1	1
Ankylosing spondylitis.....	14	11	0	3
Rheumatoid arthritis:				
Measurable soft-tissue swelling.....	15	8	3	4
No measurable soft-tissue swelling.....	37	14	14	9
Osteoarthritis.....	7	6	1	0
Miscellaneous.....	11	6	5	0
Total.....	99	58	24	17

At the beginning of the trial patients were started blind on either the drug or placebo. It was soon apparent that on the high initial dose of 300 mg. daily by mouth patients developed marked symptomatic improvement or side-effects, and, with few exceptions, were able to differentiate the true tablet from placebo. It was felt that a comparison against placebo would therefore provide less information than against other potentially anti-inflammatory agents such as phenylbutazone or the corticosteroids. In the absence of side-effects patients received a minimum of 14 days' therapy, and some have been on treatment for up to one year.

Indomethacin was used for the treatment of acute gout, ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis.

#### Gout

Fifteen patients (14 male, 1 female) with gout received indomethacin for the acute attack. It was given orally in high initial dosage and gradually reduced as symptoms and signs improved. The first four subjects received indomethacin 400–500 mg. in the first 24 hours, dosage then being reduced by 100 mg. every second day. This dose was found to require modification because side-effects occurred not infrequently and most acute attacks responded satisfactorily to a smaller amount of the drug. Subsequently 200–300 mg. was given in the first 24 hours in divided dosage, and this was gradually reduced to 100–150 mg. daily for five days, or longer if symptoms persisted. Patients were not given a maintenance dose between attacks. Plasma uric-acid estimations were performed during and after the acute attack, but these revealed no significant changes. Patients were asked to record their impression of the effect on the acute attack, the rate at which relief ensued, the extent of relief, the occurrence of side-effects, and the presence or absence of symptomatic rebound on cessation of therapy. An attempt was made to compare the response with that previously obtained from phenylbutazone, oxyphenbutazone, or colchicine.

#### Ankylosing Spondylitis

Fourteen patients with ankylosing spondylitis were treated with indomethacin. These patients had all suffered from the disease for at least two years and six had a history longer than 10 years. All had characteristic x-ray changes. All experienced considerable pain and had taken different analgesics for a long time. Ten of these patients received indomethacin 300 mg. daily in divided doses for 14 days and four received 200 mg. daily. When a steady baseline was obtained this was changed blind to placebo and rebound noted. Some patients received the placebo first. They were asked to assess their symptoms during this time and to compare the relief obtained from indomethacin with that previously obtained from phenylbutazone.

#### Osteoarthritis

Seven patients with osteoarthritis were treated with indomethacin: three of them had involvement of the hips, one severe disease in the knees, and three involvement of the cervical spine. They received indomethacin 150–300 mg. daily in divided doses for 14 days. They were asked to note any change in symptoms while on the drug and to compare this with the effect of phenylbutazone taken immediately before. Withdrawal symptoms on cessation of therapy were also noted.

#### Rheumatoid Arthritis

Patients with rheumatoid arthritis were treated with indomethacin and assessed not only on their symptomatic response but also by reduction of joint-

swelling. This group of 52 patients was divided into those exhibiting measurable inflammatory features (15) and those with less active but painful disease (37). Initially, 300 mg. was given daily in divided dosage, but subsequently 50–150 mg. daily was found to produce similar change with a lower incidence of side-effects.

The patients with inflammatory features all suffered from classical rheumatoid arthritis, 7 out of 11 having positive sheep-cell-agglutination titres ranging from 1:32 to 1:512. The method of assessment varied according to whether the patient was seen regularly as an out-patient or was admitted to hospital. In-patients were assessed by their own daily record of pain, stiffness, and morning limbering-up time. Twice weekly the size of proximal interphalangeal joints was measured by standard jewellers' rings by one observer at the same time of day. Joint tenderness over proximal interphalangeal and metacarpophalangeal joints was recorded, as was the strength of grip, using a soft cuff inflated to a pressure of 30 mm. of mercury. A Westergren erythrocyte sedimentation rate (E.S.R.) was estimated each week. In addition, four in-patients with swollen knees were assessed by daily clinical examination. Out-patients were seen weekly and the severity of symptoms was recorded, as was their range of activity. Their disease was also assessed by joint size, tenderness, and grip strength. Anti-inflammatory effect was assessed by weekly change in swelling of the proximal interphalangeal joints.

No change in the basic rest-exercise therapy was made during the trial. The patient was started on an identical placebo and observed until a steady baseline assessment was obtained; the genuine tablet was then substituted and when the new baseline was established indomethacin was withdrawn and identical placebo restarted. In assessment of the patient's condition not only an improvement on introduction of the drug was required but also deterioration when the drug was withdrawn before the clinical response was considered positive. In addition to patients with rheumatoid arthritis and inflammatory disease, 37 without measurable soft-tissue swelling were treated with indomethacin and the same parameters assessed. These patients had classical rheumatoid arthritis and the sheep-cell-agglutination titre was positive (1:32 to 1:2,048) in 22. Eight were in-patients and 29 out-patients.

#### *Miscellaneous*

Eleven patients with miscellaneous disorders were treated with indomethacin to assess its influence on fever, as in glandular fever and Reiter's disease, and pain from noninflammatory lesions such as bony metastases.

#### RESULTS

##### *Gout*

Of 15 patients with gout, 11 noted a dramatic and rapid response with full symptomatic relief, two noted a moderate analgesic response without complete alteration of symptoms, one patient noted no effect, and one developed immediate side-effects. The following case histories demonstrate the rapid response that may occur.

*Case 1.*—A man aged 52, who was diagnosed as having gout in 1956 and had acute episodes several times each year, developed an acute attack in May, 1963. Indomethacin 100 mg. t.d.s. was started. After 100 mg. he noted a dramatic improvement, and within 24 hours pain and inflammatory features had settled completely. Colchicine had produced relief in previous attacks only after several days and diarrhea had always followed. Phenylbutazone 500 mg. in 24 hours had produced some improvement, but with this drug full symptomatic control occurred only after four days or more. The patient felt indomethacin was quicker and more effective. Not all patients noted such benefit (see Case 6).

*Case 2.*—A man aged 62, who had suffered from gout since 1941, developed an acute attack involving the right carpus, the right elbow, and the left hand. After indomethacin 100 mg. he noted complete relief within four hours and was able to sleep the following night. The attack had previously been treated for four days with colchicine and phenylbutazone with little effect, and he had been kept awake at night by the pain.

*Case 6.*—A man aged 64 developed acute gout. Indomethacin 100 mg. t.d.s. resulted in mild symptomatic relief, but the joint remained painful and inflamed, and after 48 hours he developed acute gout in another joint. There were no side-effects. This may represent a failure of response, or it may that indomethacin absorption from the gastro-intestinal tract was impaired. Response in previous attacks to phenylbutazone had been entirely satisfactory.

*Case 8.*—A man aged 34 was admitted for observation after a hand injury sustained in a road accident. The next day he developed acute gout in the right ankle. Colchicine 8 mg. in divided dosage in 48 hours had no therapeutic effect and diarrhoea ensued. Indomethacin 100 mg. was given and definite relief was noted within an hour. After a further 100 mg. he was able to walk a few steps and the signs of acute inflammation were reduced. He was maintained on 300 mg. daily for five days, in which time the acute attack completely subsided. After 48 hours he developed a feeling of muzziness and headache, but this cleared on chlorpheniramine ("piriton") 4 mg. q.d.s. and on reduction of the dose to 200 mg. daily.

*Case 9.*—A man aged 50, in whom gout was diagnosed in 1956, noted no relief and no side-effects on indomethacin 100 mg. t.d.s., but obtained relief within 24 hours from 4 mg. of colchicine in divided dosage. He was the only patient who obtained no relief whatsoever from indomethacin. There seemed some doubt on his history that he took sufficient dosage to obtain therapeutic effect, for he was against taking any new drug when his old favourite, colchicine, was available.

In Table II a comparison is made between phenylbutazone and indomethacin in the seven patients who had received both drugs for the acute attack. It was suspected that Case 7 did not take the indomethacin.

TABLE II.—COMPARISON OF EFFECT OF INDOMETHACIN AND PHENYLBTUAZONE IN TREATMENT OF THE ACUTE ATTACK OF GOUT

Case No.	Indomethacin		Phenylbutazone		Preference
	Speed of action	Degree of relief	Speed of action	Degree of relief	
1	24 hours	Full	4 days	Full	Indomethacin.
2	4 hours	do	Nil	do	Do.
3	2 hours	do	do	do	Do.
4	24 hours	do	12 hours	Full	Phenylbutazone.
5	2 hours	do	24 hours	do	Indomethacin.
6	24 hours	Partial	do	do	Phenylbutazone.
7	-----	Nil	do	do	Do.

Note: The speed of action is the time between the initial dose and the onset of symptomatic relief. The degree of relief was assessed when the maximal clinical improvement had occurred. Patient 7 is suspected of not taking indomethacin.

#### Ankylosing Spondylitis

Of the 14 patients with ankylosing spondylitis who were treated with indomethacin, nine noted marked relief from pain and thought indomethacin 100 mg. was more effective than phenylbutazone 100 mg., one had moderate relief of symptoms and considered 100 mg. of indomethacin equal in effect to 100 mg. of phenylbutazone, and one noted mild improvement, less than that obtained from phenylbutazone. Except for three patients with early side-effects necessitating withdrawal of treatment, all noted deterioration on blind introduction of placebo. Three patients had side-effects which prevented assessment. The following are examples of case histories of patients who benefited from indomethacin.

A Scotsman aged 48, with ankylosing spondylitis since 1945, was experiencing severe pain in the lower back and between the shoulders. Previous therapy included phenylbutazone 300 mg. daily, which resulted in mild symptomatic relief but was associated with the development of dyspepsia. On his own initiative he started taking compound tablets of codeine in large quantities, and, although this was hard to assess, he probably took 25 tablets daily. After some weeks he was admitted as an emergency to hospital unrousable and cyanosed from excess medication. He started on indomethacin 100 mg. t.d.s., and this was increased to 100 mg. q.d.s. This dose controlled his pain to an extent that enabled him to stop taking any other treatment. On stopping indomethacin he deteriorated to his previous state.

A man aged 38, who was diagnosed in 1952 as having ankylosing spondylitis, had episodes of severe low-back pain lasting from 10 to 21 days, with full remission of symptoms between attacks. On starting phenylbutazone 100 mg. b.d. he had partial relief of symptoms after three days. Any increase in dosage produced a rash. Indomethacin 100 mg. b.d. controlled symptoms completely within 48 hours.

A woman aged 27, with ankylosing spondylitis and peripheral joint involvement, was maintained on 12 units of corticotrophin daily. Indomethacin 100 mg.

t.d.s. produced a marked improvement in pain and corticotrophin was reduced by 5 units a day. Within two days she developed a severe headache; indomethacin was withdrawn and symptomatic deterioration ensued. Corticotrophin was increased to the original dose level and symptoms improved only slightly; a further temporary increase of 5 units a day was required before her clinical condition was adequately controlled. Subsequently she was found to have a good clinical response to indomethacin 50 mg. once or twice a day, dizziness on 50 mg. t.d.s., and headache on 100 mg. t.d.s.

#### *Osteoarthritis*

Six of seven patients with osteoarthritis noted symptomatic relief. Four out of five in whom a direct comparison was made preferred indomethacin to phenylbutazone. One patient noted no change in symptoms.

#### *Rheumatoid Arthritis*

Eleven patients with rheumatoid arthritis with measurable inflammatory features were assessed. Eight were out-patients and three were in-patients. In addition, four in-patients with swelling of the knees were included, making a total of 15 patients with active inflammatory disease (Table III). Of these 15 patients, eight showed clinical improvement with reduction in joint-swelling and two were inconclusive in that no rebound occurred on cessation of therapy. The following are examples of patients who improved clinically and noted reduction of joint-swelling.

A woman aged 58, with rheumatoid arthritis of two years' duration (Fig. 1), was severely incapacitated by pain, and the knees in particular had deteriorated to such an extent that she spent much time in bed and did not go out of doors. She was maintained on prednisone 20 mg. a day and aspirin 60 gr. (4 g.) a day. Indomethacin 300 mg. a day produced a marked clinical improvement and reduction in ring size. When she was changed blind to placebo she deteriorated to such an extent that the house-physician, who did not know of the alteration, ultimately used pethidine for analgesia. On reintroduction of indomethacin she improved once more, and after five weeks was discharged greatly improved and able to take short walks. She has been on indomethacin for a year with sustained improvement and with no side-effects. She had previously had a partial gastrectomy for duodenal ulceration and was able to tolerate indomethacin satisfactorily. Butazolidin had been ineffective in dosage of 300 mg. a day.

A 38-year-old woman developed rheumatoid arthritis at the age of 36. Neither paracetamol nor aspirin produced significant symptomatic improvement. Indomethacin 100 mg. b.d. gave her a feeling of drunkenness after 24 hours, but this disappeared on 50 mg. t.d.s. Placebo was introduced blind and assessment showed deterioration; improvement occurred on reintroduction of indomethacin.

TABLE III.—EFFECT OF INDOMETHACIN COMPARED WITH THAT OF PHENYLBUTAZONE IN ANKYLOSING SPONDYLITIS AND RHEUMATOID ARTHRITIS

Disease	Number of patients	Better than Phenylbutazone	Equivalent to Phenylbutazone	Less effective than Phenylbutazone	Inconclusive
Ankylosing spondylitis.....	14	9	1	1	3
Rheumatoid arthritis:					
With measurable soft-tissue swelling.....	15	8	.....	3	4
With no measurable soft-tissue swelling.....	37	9	4	15	9

Five patients failed to show reduction in ring sizes on indomethacin. In two the explanation was probably that treatment was given for too short a time to cause much change, as it had to be stopped after a few days because of side-effects. Two patients probably did not respond because there was inadequate initial acute oedema to show measurable change. The fifth patient responded to corticosteroids but not to indomethacin.

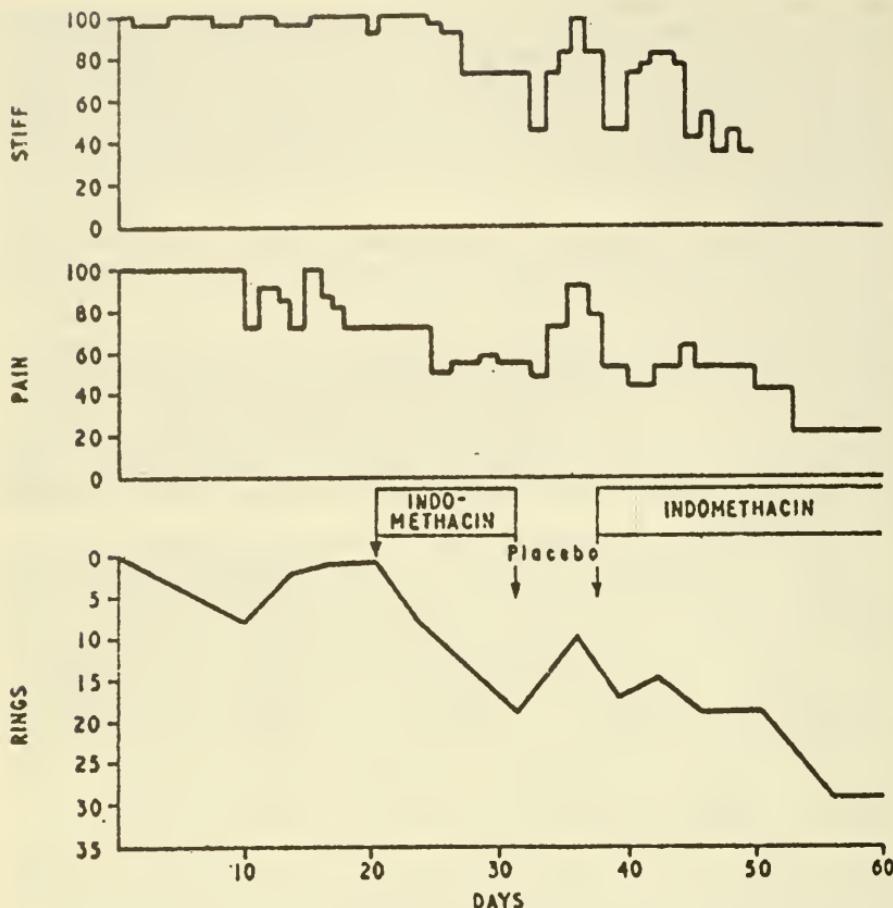


FIG. 1.—Chart of woman aged 58 treated with indomethacin for rheumatoid arthritis of two years' duration.

A man aged 61 developed acute rheumatoid arthritis over a period of nine months and required admission to hospital. As can be seen in Fig. 2, his condition was not improved by salicylates. Indomethacin was introduced without any pronounced effect and he was changed to corticotrophin. This resulted in clinical improvement and marked loss of inflammatory swelling.

In this case the rheumatoid disease was very active and a dosage of 60 units of corticotrophin was required initially to control the condition. In five cases where both drugs were used corticotrophin proved a much more effective anti-inflammatory agent than the new one.

Of 37 patients with rheumatoid arthritis without measurable inflammatory features, 14 noted a beneficial effect, 14 noted no effect, and in 9 the result was inconclusive. Of the 14 patients who noted a good effect 9 preferred indomethacin (100 mg.) to phenylbutazone (100 mg.), four noted a moderate improvement, equivalent to that obtained from phenylbutazone, and one noted mild symptomatic relief only. Of the 14 patients who noted no improvement on indomethacin, six benefited from phenylbutazone, while seven noted no effect; one had not received phenylbutazone. Indomethacin was inconclusive in a further nine patients, eight of whom experienced side-effects and one developed an influenza-like illness and stopped taking the tablets. Six of these patients found phenylbutazone to be of value, two noted no effect, and one had never taken phenylbutazone.

## SIDE-EFFECTS

Side-effects were frequent with indomethacin on a dosage of 300 mg. daily, occurring in 26 of 50 patients. Reactions at this dose level usually occurred 48 to 96 hours after starting treatment. Seven patients who experienced side-effects on 200-300 mg. a day were found to be symptom-free on a smaller dose more gradually introduced.

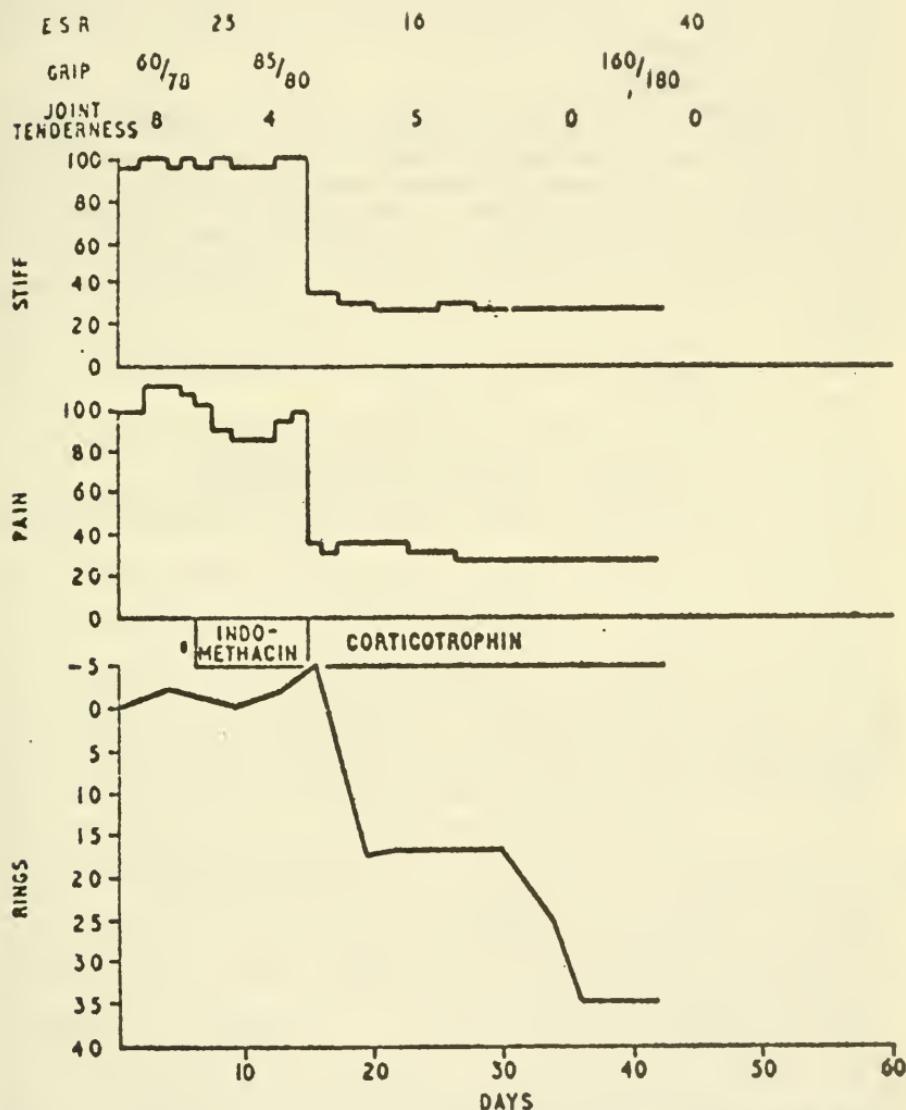


FIG. 2.—Chart of man aged 61 treated with indomethacin for acute rheumatoid arthritis with little effect.

*Gout*

Of 15 patients who received indomethacin for the acute attack of gout, three experienced side-effects. One developed a headache after 48 hours on 300 mg. daily, which cleared on 200 mg. a day and was relieved by an antihistaminic preparation. Another patient noted mild headache and giddiness on 400 mg.

daily after 48 hours. Only one patient had a severe but transient reaction. This woman, aged 23, had hyperuricaemia, a family history of gout, and congenital hypoplastic kidneys, and was subject to acute gout. Her blood urea was 52 mg./100 ml. and uric acid 13.2 mg./100 ml. She took indomethacin 100 mg. for an acute attack of gout and within 10 minutes became drowsy, was unable to focus on any object, and later developed a severe throbbing headache. Symptoms improved after four hours, but the headache remained for 24 hours. Several cups of coffee reduced her drowsiness. The reaction was thought to be too rapid in onset to be accounted for by high blood levels of indomethacin due to impaired renal function. This was an abnormal incident, no similar reaction being observed in any other patient.

#### *Rheumatoid Arthritis*

Of the 52 patients with rheumatoid arthritis who received indomethacin 31 noted side-effects. The age of these patients varied from 20 to 56. Symptoms developed within two to three days in 16. They occurred within six hours of the first dose in 10, and in five reactions were delayed until after six days. Patients usually experienced several side-effects at the same time. Of 37 patients with relatively inactive rheumatoid arthritis, 28 experienced side-effects, while only 3 of the 15 patients with measurable inflammatory disease were affected.

*Headache* occurred in 14 of 31 patients. This was characteristically a generalized throbbing in the head and ears; one was severe, eight were moderate, and five mild.

*Giddiness* was present 12 patients. This was a sensation of unsteadiness without vertigo. It interfered with gait and driving a car. Three were mild, eight moderate, and one was severe.

*Faintness*, coupled with a sense of impending loss of consciousness, was experienced by two patients. This symptom occurred only when other side-effects were pronounced. In no case, however, was there loss of consciousness.

*Muzziness and mental change*: two patients noted muzziness with inability to concentrate or think out intellectual problems. Two felt emotionally detached, and four said they felt drunk.

*Nausea and vomiting*: nine patients experienced anorexia and nausea, two of whom vomited.

*Diarrhoea*: four patients experienced diarrhoea. This was usually associated with nausea or vomiting.

*Dyspepsia*: four patients experienced dyspepsia, which was severe and necessitated cessation of treatment: one had no previous gastro-intestinal history, two were intolerant of phenylbutazone, and one, who had both a hiatus herina and gall-stones, developed dyspepsia with soluble aspirin, paracetamol, and placebo tablets identical in appearance to indomethacin. Two patients developed dyspepsia within two days of starting the drug and the other two first noted symptoms after seven days' therapy.

*Drowsiness*: two patients developed drowsiness within one hour of the first dose. If they sat down they fell asleep. This symptom occurred only after the more severe reactions and was improved by taking coffee. Blurred vision was noted by these patients.

Side-effects usually cleared within 24 hours of cessation of treatment, but occasionally lasted for two to three days. Five patients were given anithistamines, chlorpheniramine 4 mg. q.d.s., and four noted improvement in the headache but not in gastro-intestinal symptoms.

The effect of a lower dose on side-effects has been studied in seven patients intolerant of high dosage. Of three patients who experienced side-effects on 300 mg. a day, two were symptom-free on 200 mg. and one on 150 mg. a day. Three patients with side-effects on 200 mg. daily were able to tolerate 150 mg. a day, and one of these who suffered side-effects on 100 mg. b.d. was found to become symptom-free on 50 mg. q.d.s. One patient, intolerant of 100 mg. a day, was maintained satisfactorily on 50 mg. a day.

#### *Anklosing Spondylitis and Osteoarthritis*

Six of the fourteen patients with anklosing spondylitis developed side-effects; four were taking 300 mg. a day, one of whom later had no symptoms on 200 mg. a day; one was on 200 mg. a day; and one on 100 mg. a day, experienced a mild headache.

Of seven osteoarthritic patients treated none noted side-effects.

## PATTERNS OF SIDE-EFFECTS

Of 88 patients with disorders of the locomotor system treated with indomethacin, 40 (45.4%) suffered side-effects. These effects were commoner in patients with rheumatoid arthritis (59.6%) than with gout (20%). Side-effects included headache, giddiness, faintness, muzziness, mental change, anorexia, nausea and vomiting, dyspepsia, diarrhoea, drowsiness, and blurred vision. More than one symptom occurred in all patients. Headache was improved by antihistamines, and drowsiness by coffee. Seven patients with rheumatoid arthritis and one with ankylosing spondylitis who had side-effects on relatively high initial dosage were found to be symptom-free on a lower dose more gradually introduced. It is probable, therefore, that with a starting dose of indomethacin 50 mg. daily and gradual increase by 50 mg. every third day to a maximum of 200 mg., the incidence of side-effects may be much lower than this figure. A dosage of 300-500 mg. daily may occasionally be used, but side-effects are likely to be frequent. There was no evidence of toxic effect on the blood, liver, or kidneys.

Side-effects occurred in four patterns: (1) Within a few hours the patient experienced severe symptoms independent of the dose. (2) Side-effects developed most often between 48 and 72 hours and were reduced by adjusting the dose. This appears to be a cumulative effect. (3) A small number of patients developed symptoms after seven days, as in two of the four cases of dyspepsia. (4) Some patients experienced muzzy feelings and mild headache about two hours after each dose, which wore off after an hour and did not progress. This occurred only with the 100-mg. tablet, never the 50 mg.

## DISCUSSION

It is clear that in indomethacin we have an agent that will reduce swelling and also relieve pain. As an anti-inflammatory agent it is less effective than the corticosteroids and corticotrophin, but it is the only non-steroid agent we have used to date which has produced measurable reduction in finger-swelling in active rheumatoid arthritis. In this disorder those cases with measurable inflammatory swelling did appreciably better and had fewer side-effects than those with less inflammatory change. In two cases the dose of corticosteroids previously needed to control symptoms was gradually reduced under cover of the new drug, but in 12 others it proved ineffective. The response in acute gout is, in our opinion, better than with any other therapeutic agents at present available, for its action is more rapid than that of phenylbutazone and the patient is less subject to rebound attacks than with corticotrophin. The definite relief of pain in the few cases of osteoarthritis assessed makes it seem likely that the drug has analgesic properties independent of its anti-inflammatory ones, and its use in a few febrile cases demonstrated that it is also an effective antipyretic: in one case of glandular fever treated with indomethacin there was rapid improvement in symptoms and signs, with relapse as soon as it was discontinued.

As regards toxicity, it is clear that our initial dosage was too high and we now seldom use 100-mg. tablets, but favour 50 mg. one to four times daily. On this lower dosage side-effects are much less troublesome and the headache and muzziness which are the commonest complaints often pass off on continuation of low-dosage therapy. Many patients intolerant of other drugs because of gastrointestinal side-effects are tolerant of indomethacin, which in our hands has proved relatively non-toxic in this respect to man, unlike the results in experimental animals. Time will show if there are any other side-effects, but at present no changes in blood counts or liver- or renal-function tests have been noted, nor were skin reactions seen. We have not used it in children or in pregnant women. On present evidence we consider that indomethacin, in spite of its tendency to cause headaches and dizzy feelings, has a definite part to play in the treatment of the chronic rheumatic disorders, and we regard it as the drug of choice in acute gout. In ankylosing spondylitis, osteoarthritis, and active rheumatoid arthritis it has also much to offer.

## SUMMARY AND CONCLUSIONS

Indomethacin (*1-p-chlorobenzoyl*-5-methoxy-2-methylindol-3-acetic acid) has proved to have anti-inflammatory and pain-relieving effects in gout and rheumatoid arthritis. It has also proved effective in the treatment of ankylosing spondylitis and osteoarthritis. As a dosage about 200 mg. a day headaches and dizziness were frequent, occurring in over 50% of those treated. At a daily dosage of 50-200 mg. side-effects occurred in 43%.

Dyspepsia has been rare—in 4 out of 99 patients. Also rare were faintness (2), drowsiness (2), and feelings of drunkenness (4). Intolerance or resistance to the drug has not been observed in up to one year of continuous treatment.

Indomethacin is the drug of choice in acute gout, where relief is obtained more rapidly than with phenylbutazone. It is useful also in ankylosing spondylitis, in osteoarthritis, and in cases of rheumatoid arthritis with inflammatory features and swelling of joints.

Although more time is needed before the true incidence of toxic effects can be evaluated, indomethacin appears to be a useful addition to the treatment of these rheumatic disorders.

#### ADDENDUM

We have now followed up 123 patients for periods of up to one year; other workers have reported dyspepsia and occasional gastrointestinal haemorrhage as complications of indomethacin therapy. In our experience to date, only 4 out of 123 patients have experienced dyspepsia and none has had clinically detectable haemorrhage. Three of these four patients have suffered dyspepsia on phenylbutazone.

One patient who noted an initial symptomatic improvement on indomethacin has found that the symptoms have gradually returned in spite of continued treatment. This was thought to be due to the possible development of tolerance.

Three out of 123 patients developed skin lesions; one of these suffered from disseminated lupus erythematosus. The rash was irritating and consisted of discrete red macules and papules on the limbs. It disappeared completely within 48 hours of stopping the drug.

In one patient a reduction of the drug from 350 to 150 mg. a day resulted in the rash resolving.

We wish to thank Dr. J. Merry and Dr. R. Hodgkinson, of Merck Sharp and Dohme, for their co-operation and for the provision of supplies of indomethacin; also Dr. D. Taylor, of St. Stephen's Hospital, Chelsea, who was responsible for the clinical care of some of the patients.

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#### INDOMETHACIN AND PHENYLBUTAZONE: A COMPARISON

(By F. Dudley Hart,\* M.D., F.R.C.P., and P. L. Boardman,\* M.R.C.P.)

Early papers on indomethacin reported promising results from its use as a non-specific anti-inflammatory agent in the treatment of the chronic rheumatic disorders (Paul and Strottman, 1963; Ballabio *et al.*, 1963), with dramatic results in gout (Smyth *et al.*, 1963). A controlled clinical trial demonstrated significant preference for indomethacin against placebo in rheumatoid arthritis (Dixon *et al.*, 1963). Measurable reduction of joint swelling as a result of treatment with indomethacin was reported in active rheumatoid arthritis (Hart and Boardman, 1964). There was no significant difference between indomethacin and phenylbutazone (Percy *et al.*, 1963)—in this trial the treatment period on each drug was one week and the indomethacin used was in tablet form, which, for various reasons, has been replaced by a gelatin-coated capsule.

This paper reports the results of a double-blind trial in which the effect of phenylbutazone is compared with that of indomethacin capsules, each drug being given for one month to patients with active rheumatoid arthritis. A brief account is also given of the results obtained from the treatment of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis with indomethacin during a period of two and a half years.

#### I. DOUBLE-BLIND TRIAL

All 26 patients who took part in the double-blind trial of indomethacin and phenylbutazone had classical rheumatoid arthritis or definite rheumatoid arthritis as defined by a Committee of the American Rheumatism Association (1959).

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The diagnosis of the classical form of the disease is applied to those patients in whom 7 out of the 11 criteria listed by the A.R.A. are present. A diagnosis of "definite" requires the presence of five of the criteria. Phenylbutazone, 100 mg. three times a day, was given to 13 patients in the first months, and indomethacin, 25 mg. three times a day, to 13, therapy being changed to the other agent at the end of the month. To provide double-blind conditions they received active indomethacin and dummy phenylbutazone in one month, and in the other active phenylbutazone and dummy indomethacin. The group who started on indomethacin had a mean age of 47.6 years; five were males and eight females. The mean duration of disease was 6.7 years. The patients who received phenylbutazone in the first month had a mean age of 48.8 years, an average length of history of 6.2 years, and there were four males and nine females. There were six patients with classical and seven with definite rheumatoid arthritis in each group. These patients were assessed by their own daily record of pain, stiffness, and loosening-up time, and the measurement of joint tenderness, joint swelling, and grip strength at each visit (Hart and Boardman, 1963). All were attending the out-patient clinic at monthly intervals. They were assessed at the start of treatment and at the end of each trial period of 28 days. Their personal opinion as to the more satisfactory treatment period was recorded at the end of the trial.

#### RESULTS

When asked at the end of the trial, before the identification of the specific treatment periods, which month was the more satisfactory, 15 patients preferred phenylbutazone, 10 found them to be equally effective, and one preferred indomethacin. This difference is statistically significant ( $P < 0.001$ ).

A comparison of the pain record of each patient in the month on phenylbutazone with that of those on indomethacin revealed that this parameter improved selectively in five in phenylbutazone and in two on indomethacin, 19 finding no difference. A clinically significant alteration of pain was taken to be 25% or more in the month. Likewise, assuming a 25% difference to be significant, five were less stiff during phenylbutazone therapy and one on indomethacin, 20 finding no detectable difference. There is obviously no significant difference in these symptoms between the two groups.

An alteration in the duration of early-morning stiffness was assumed to be of clinical significance if it exceeded 30 minutes. In the first month, on phenylbutazone, there was improvement in the loosening-up time in seven patients and deterioration in one, five being unchanged. On indomethacin there was improvement in three, deterioration in four, and no change in six. These changes are not statistically significant ( $\chi^2 = 1.4$ ;  $n = 1$ ;  $0.3 > P > 0.2$ ). In the second month, on indomethacin, improvement occurred in three patients, and this parameter worsened in two, eight exhibiting no change. On phenylbutazone there was no change in six, four improved, and three deteriorated.

A difference in grip strength of 50 mm. of mercury was assumed to be clinically significant. In the first month, on phenylbutazone, none improved, five deteriorated, and eight remained unchanged. On indomethacin three improved, one deteriorated, and there was no change in nine. There was no statistically significant difference between the groups ( $\chi^2 = 1.5$ ;  $n = 1$ ;  $0.3 > P > 0.2$ ). In the second month, on indomethacin, 11 patients remained unchanged, one improving, and one deteriorating. In comparison, on phenylbutazone, there was no change in 10 patients, improvement occurring in three. There was obviously no significant difference.

As 17 of the 26 patients had no tender joints at any time during the trial this was an unsatisfactory parameter.

Assuming a change of three ring sizes in joint size to be significant, there was no difference in 17 patients, five were better on indomethacin, and four on phenylbutazone. The improvement in joint size, in the first month, in the patients on phenylbutazone, was by four rings. On indomethacin the improvement was by 35 rings. This difference is not statistically significant ( $t = 1$ ;  $n = 24$ ;  $0.2 > P > 0.1$ ). In the second month indomethacin was associated with an improvement of 21 ring sizes, compared with 17 on phenylbutazone.

#### II. LONG-TERM STUDIES

Ninety-seven out-patients and 21 in-patients with classical or definite rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis were treated with indomethacin. In some cases it was possible to compare results with those previously obtained with pyrazole derivatives.

*Rheumatoid Arthritis*

Ninety-seven out-patients and 21 in-patients with classical to definite rheumatoid arthritis (American Rheumatism Association Committee, 1959) were followed up for two and a half years. Ninety were females and 28 males. Their average age was 53.3 years, and the mean duration of rheumatoid arthritis was 8.1 years. The sheep-cell-agglutination titre was positive in 85 patients.

The in-patients were assessed by their own daily record of pain, stiffness, and the duration of early-morning stiffness, together with twice-weekly estimations of grip strength, joint tenderness, and joint size (Hart and Boardman, 1963). Identical placebo was administered to conceal the exact time of the start and the withdrawal of indomethacin by blind substitution. The E.S.R. was measured weekly. Four grades of response were recognized in the out-patients with rheumatoid arthritis, according to the criteria of therapeutic response defined by the American Rheumatism Association Committee (Steinbrocker *et al.*, 1949, recorded in this paper as good, fair, poor, or nil; the E.S.R. was excluded from this assessment. In all patients in whom treatment had included a pyrazole derivative indomethacin was compared with phenylbutazone or oxyphenbutazone, their relative effectiveness being recorded at arbitrary maintenance dosage. This was 300 mg. daily for the pyrazoles, 200 mg. daily for indomethacin tablets, and 75 mg. daily for the capsule preparation. The prolonged effect of indomethacin was checked by the observation of rebound deterioration on withdrawal of the drug.

*Osteoarthritis*

With one exception the 52 patients with osteoarthritis were treated in the out-patient clinic. They included 35 females and 17 males with an average age of 61.2 years and a mean duration of symptoms of 4.5 years. A good response was one with 85% control of symptoms as assessed by the sufferer, the residual pain constituting minor discomfort only and not interfering with daily activity. A fair response was one in which there was therapeutically useful improvement but not to the extent of removing all serious discomfort. A poor response was one in which there was some slight symptomatic improvement, insufficient to be of therapeutic value.

*Ankylosing Spondylitis*

There were 26 males and six females in the group of 32 patients with ankylosing spondylitis, the average age being 37.6 years and the mean duration of disease 13.4 years.

## RESULTS

*Rheumatoid Arthritis In-patients*

Pain and stiffness were reduced in 15 of the 21 in-patients, there being no change in five and side-effects in one. Early-morning stiffness improved in eight, remained static in six, and was too short initially for assessment in six; in one patient side-effects prevented assessment.

Grip strength improved by more than 50 mm. of mercury in seven patients. It improved slightly in one patient, remained unchanged in six, and was an unsatisfactory parameter in seven—in five as a result of side-effects, and in two because of lack of involvement of the hands. Joint tenderness improved in five patients, was unchanged in two, and side-effects interfered in five; in nine there were no tender joints.

Compared with the baseline, there was reduction of joint size on indomethacin of 79 ring sizes in seven patients, while three deteriorated by 11 ring sizes. There was no change in five. Assessment was unsatisfactory in six because of side-effects and lack of involvement of the hands.

There was no significant change in the E.S.R. in response to the administration of indomethacin.

Of the 21 in-patients 19 had previously received a pyrazole derivative. The preference was for indomethacin in six, and for phenylbutazone or oxyphenbutazone in four; nine patients were unable to detect significant difference.

*Rheumatoid Arthritis Out-patients*

In the 97 out-patients the response to indomethacin was good in 28, fair in 21, poor in 10, and nil in 38 patients. A comparison with a pyrazole derivative was possible in 80 patients. Indomethacin was preferred by 30, a pyrazole derivative by 19, and they were found to be equally effective in 31 patients.

*Ankylosing Spondylitis*

The response to indomethacin in the 32 patients with ankylosing spondylitis was good in 16, fair in six, poor in one, and nil in nine. In 19 patients the treatment of choice was indomethacin, and in nine it was phenylbutazone or oxyphenbutazone; four patients considered them to be of equal value.

*Osteoarthritis*

The response to indomethacin in the 52 patients with osteoarthritis was good in 30, fair in four, poor in seven, and nil in 11. It was possible to compare indomethacin with the pyrazoles in 39 patients. Indomethacin was the drug of choice in 15 and phenylbutazone or oxyphenbutazone in 13; 11 found them equally satisfactory.

## SIDE-EFFECTS

Side-effects occurred in 104 of the 202 patients treated with indomethacin (51.48%); this consisted of 67 out of 101 (66.3%) on indomethacin tablets, and 37 out of 101 on capsules (36.6%).

The following complaints were noted, the incidence being recorded in brackets: headache (46), giddiness (25), dyspepsia (16), muzziness (16), nausea (12), vomiting (5), rash (4), diarrhea (4), felt odd (2), sleepy (2), heavy legs (2), drunk (1), faint (1), mouth ulceration (1), unpleasant taste (1), depression (1), lassitude and nightmares (1), swollen tongue (1), constive (1), and shakiness (1).

In 88 patients side-effects occurred within seven days of starting indomethacin, in nine patients within seven to 14 days, and in two patients between 14 and 21 days. Side-effects occurred after three weeks in five patients only.

Dyspepsia occurred in 16 of the 202 patients (7.92%). In contrast, of the 170 patients who received a pyrazole agent 40 had dyspepsia (23.5%). In no patient was there overt evidence of gastro-intestinal haemorrhage, and none developed perforation. One patient with rheumatoid arthritis and one with osteoarthritis of the hip had slow gastro-intestinal blood loss, the administration of indomethacin being associated with a fall in the haemoglobin by 20–40% within a month.

Barium studies were available for 16 patients, all of whom had dyspepsia on phenylbutazone or oxyphenbutazone and eight on indomethacin. A duodenal ulcer was detected in seven patients, all intolerant of pyrazoles; indomethacin was tolerated by four of these patients and caused dyspepsia in three; these seven have received 995 patient days of treatment with indomethacin to date. In five patients with demonstrable gastric ulcers—one with a hiatus hernia also—all intolerant of phenylbutazone, indomethacin was associated with dyspepsia in one, being well tolerated in four patients; this group has received 571 patient days of treatment to date without serious gastro-intestinal complications. In three patients no abnormality was detected on barium-meal examination. All three were intolerant of phenylbutazone; indomethacin was associated with dyspepsia in two patients, and in one may have been the cause of anaemia by slow continuous blood loss. One patient, with both a hiatus hernia and gall-stones, suffered from dyspepsia on indomethacin, phenylbutazone, salicylates, and placebo.

## DISCUSSION

It is increasingly apparent that the therapeutic effect of indomethacin has many similarities to that of phenylbutazone, irrespective of the mode of action. Though painful symptoms are relieved by phenylbutazone, the action being remarkably even throughout the 24 hours, reduction of joint swelling occurs in only occasional cases of rheumatoid arthritis. The regular, predictable reduction of joint size with the corticosteroids, offset by the untoward affects of prolonged therapy, suggested that the advent of a new non-steroid preparation with this property would be a considerable advance. Of the many preparations tried in the last 17 years at the Westminster Hospital (F.D.H.) indomethacin has been the first non-steroid drug to produce a measurable reduction in joint size in selected cases of active rheumatoid arthritis. The spectrum of side-effects on indomethacin overlaps phenylbutazone slightly with respect to the gastro-intestinal tract but is otherwise quite different. It is possible that the response to indomethacin is not as consistent as that obtained from phenylbutazone over the 24 hours; in this series the overall response was slightly less than 60%.

The double-blind trial confirmed that, under defined conditions, there was no significant difference between indomethacin, 75 mg. daily, and phenylbutazone, 300 mg. daily, in the relief of pain and stiffness in rheumatoid arthritis. Though the alteration of joint size on the two drugs was not statistically significant, the

trend in each group suggested that this parameter improved specifically on indomethacin. The magnitude of the response obtained depends not only on the anti-inflammatory effect of the administered drug but also on the amount of soft-tissue inflammatory swelling present that is potentially capable of exhibiting reduction of size. It is unlikely that optimal conditions existed in these patients, for reduction of joint size; they were selected from the regular attenders at the out-patient clinic and had disease of moderately long duration. That indomethacin was associated with reduction of joint size, as compared with the baseline, was demonstrated in the patients admitted to hospital.

Indomethacin was initially available in the form of tablets. These proved to be unsatisfactory and gelatin-coated capsules were substituted. The patients in the long-term studies received both preparations. These results are not given separately, except for side-effects, because the capsule is the only preparation available; a comparison of the two preparations revealed that the only difference of statistical significance was the incidence of side-effects.

The most consistently satisfactory results from indomethacin were obtained in patients suffering from ankylosing spondylitis (68.7%) and osteoarthritis (65.3%). Results for gout are reported separately (Boardman and Hart, 1965). Excellent results did occur in rheumatoid arthritis, in particular in patients with active disease, but there were also some dramatic failures, and overall benefit was obtained in only 50.5%.

Side-effects were a more frequent cause of therapeutic failure than inadequate drug potency. The change from the tablet to the capsule preparation was associated with a reduction in frequency from 66.3% to 36.6%, together with a decrease in the severity of untoward reactions. The most common pattern of side-effects consisted in headache, giddiness, muzziness, and nausea. These were transient, dependent on dosage, and occurred within the first few days of starting treatment.

Dyspepsia was relatively rare during indomethacin administration. Smyth *et al.* (1964), in a study of 63 patients with rheumatoid arthritis during an 18-month period, found one who developed peptic ulceration on indomethacin and one on placebo. Catoggio *et al.* (1964) had two cases of duodenal ulceration in a group of 33 patients. Clark (1964), in a study of 100 patients with rheumatoid arthritis, encountered peptic ulceration in 10, nine of whom also received corticosteroids; there were three instances of perforation and one of hemorrhage. Bilka *et al.* (1964) reported one patient, out of a total of 61, who developed a small gastric ulcer after 12 weeks of indomethacin therapy. Haemorrhage and perforation do not appear to be serious risks as judged on the figures of this series, in contrast to the findings of Lövgren and Allander (1964). Unlike their six patients with a history of gastric or duodenal ulceration treated in hospital, in our series four of seven patients with duodenal ulceration and four of five with gastric ulcers tolerated indomethacin well, the total period of therapy being 1,566 days. Nevertheless, with certain exceptions, dyspepsia occurring on indomethacin was considered an absolute indication for cessation of therapy. In our series antacids were not used for symptomatic control. Lövgren and Allander (1964) treated their patients in hospital with anticholinergics and antacid agents; it is possible that some of their problems arose as a result of the masking effect of these symptomatic remedies on what should be considered a warning symptom.

The dose probably suitable for most patients is 25 mg. three times a day, administered after food. It is suggested that to overcome the frequent early side-effects the dose should be increased slowly during the first week, from an initial 25 mg. daily. Dyspepsia due to indomethacin is an indication for the withdrawal of therapy.

During the two and a half years that indomethacin has been available to us it is of relevance to note that only three patients with rheumatoid arthritis have been started on long-term corticosteroid therapy or A.C.T.H. The fact that a non-steroid anti-inflammatory agent is now available may well make a profound difference to the present use of corticosteroids in this condition.

#### SUMMARY

A double-blind cross-over trial was carried out to compare indomethacin, 75 mg. daily, with phenylbutazone, 300 mg. daily, each being given for a period of 28 days to patients with active rheumatoid arthritis. No significant differences were found between the two groups in the relief of symptoms, but the results

obtained were indicative of greater reduction of early-morning stiffness on phenylbutazone and of joint swelling on indomethacin. The personal preference, expressed at the end of the trial, was in favour of phenylbutazone.

In a mixed group of patients treated over two and a half years indomethacin was effective in improving the symptoms of osteoarthritis (65.3%) and of ankylosing spondylitis (68.7%). In rheumatoid arthritis failures were more frequent, a satisfactory response being recorded in 50.5% of cases.

Side-effects on indomethacin capsules, at an average maintenance dose of 75 mg. daily, occurred in 36.6% of patients in the mixed group. The common side-effects were headache, giddiness, muzziness, nausea, and vomiting. Dyspepsia was not a major problem, occurring in 7.92% of patients; it was only rarely dose-dependent and occurred at any time during long-term administration in contrast to the other side-effects, which were dependent on dose and developed almost always within the first 14 days of treatment.

#### ADDENDUM

Since the completion of this study, one patient on indomethacin, 200 mg. daily, and prednisolone, 8 mg. daily, with a history of duodenal ulceration, present 20 years earlier, developed dyspepsia after six months on indomethacin. This was followed by a haematemesis which required blood transfusion. In many of the cases of haematemesis reported this combination of drugs was used.

We would like to thank Dr. R. Hodgkinson, of Merck, Sharp, and Dohme Ltd., for generous supplies of indomethacin.

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**Senator NELSON.** This is probably a question for Mr. Goodrich.

As you know, all of these drugs are handled and promoted by detail men. What legal control, if any, do you have over the information presented by detail men to the physician?

**Mr. GOODRICH.** Basically our control would be over the detailing pieces—the written, printed and graphic materials that the company develops to be used as detailing pieces. As we move into some of the drugs, particularly Vibramycin which is coming up later, a detailing piece is one of the major pieces there we will be going over with you.

In addition to that, the regulations require that all promotions, whether it be advertising, direct mailings, promotional material left by the detail man, must all conform to the approved labeling, and must all present the full disclosure of both the good and the bad about the drug.

Now, in terms of what the detail man says in the doctor's office, legally we could do something about that. But as a practical matter, we have no means of regulating that unless the doctor who is detailed tells us what happened and is willing to be a witness.

You will remember that in the hearings on Chloromycetin before the Kefauver committee, there was one instance in which one of our own men, one of our own physicians who was in private practice, was detailed by the company for Chloromycetin, and we did communicate with the company immediately about that improper detailing, and they represented that they had corrected it.

But we have no program of monitoring what the detail men say.

Now, we do have physicians attending meetings, and observing exhibits around the meetings, who hear the detailing of a public nature. In those instances, any time an oral advertising claim is made which exceeds the permissible bounds of the approved labeling, this results in the product being misbranded for failure to bear adequate directions for use.

**Senator NELSON.** If my recollection is correct, those who have commented on this question before the committee felt that the detail man is frequently quite effective in influencing physicians' prescribing habits. I am wondering how you, the FDA, can control the advertising that goes to the doctor and be effective yourself if one large aspect of the promotion of the drug, that is, the detail man, is not effectively controlled?

**Mr. GOODRICH.** This is certainly a problem, Senator. But if we can be successful, as we hope we are, moving in this direction, in providing assurance that publications such as *Physicians' Desk Reference*, which is on the doctor's desk, all the advertisements in the journals, the mailing pieces that go out, fairly comply with the requirements of the law, either by providing full disclosure in case of mailing pieces and adequate brief summary in case of journal advertising, that the physician who is detailed certainly has a place to turn where he can be adequately and completely informed about the drug, to have a basis on which he can make a comparison with the detail man's claim.

Another point is that PDR is a limited volume, as we all know, and this is one of the reasons we are advocating the bill you yourself introduced, to have a reliable compendium which will provide every doctor's office on his desk complete, reliable, adequate information on drug prescribing.

**Senator NELSON.** Do you evaluate and pre-evaluate the literature that the detail man is permitted to give to a doctor?

**Mr. GOODRICH.** We do not. We certainly have the right to, and do, look at a good deal of this, that is promotional material. The companies are required to submit with their records and reports the promotional material that is being used—not every piece, because they are quite voluminous. But any piece that—any promotional piece that is different in any significant way from one that has already been submitted is required to be submitted.

That does not mean that Dr. Ley's group adequately reads all that material, because its volume, even in terms of not being complete—not being the complete outpouring of promotion—the volume that we receive, only part of the total, is still quite large, and more than we can handle with our present people.

Senator NELSON. Do they hand out this type of promotional piece and so forth, like the JAMA ads?

Mr. GOODRICH. Sure. The same kind. You will see in the ads you have before you some of them run several pages—it is not unusual to see an elaborate ad running several pages, that is suitable for reprinting, either for direct distribution or handout by the detail man. The companies also use attractive visual aid type of promotional material to make their detailing more effective. And they use a great many other promotional techniques. I am constantly amazed at the creativity of the people on Madison Avenue who think up these ideas. But they certainly have a lot of ways of getting the message across. It could not be better stated than you did, that the problem of competing with a message such as the ad you have in front of you is a difficult problem.

Senator NELSON. In the event that some promotional material being handed to the doctor by the detail man exceeds the claims in the package insert, do you have the authority to make them correct it?

Mr. GOODRICH. Yes, sir.

Senator NELSON. Do you ever do that?

Mr. GOODRICH. Oh, yes.

Senator NELSON. You say the material is very massive. You do not review it all—or do you?

Mr. GOODRICH. We just physically cannot review it all. I would certainly recommend a substantial increase in the amount of effort we have on this. But Dr. Ley is the one who has to put the medical resources into it, and I believe the judgment has been made by him and by Dr. Goddard that we are at the level of maximum now that we can put into it—although it could stand some more help.

Senator NELSON. Do you require the detail man to submit any piece of literature, the contents of which you regulate, like the package insert, to the doctor on each occasion that he is detailing the drug?

Mr. GOODRICH. Only in the sense that every piece of written material, written, printed, or graphic material that he leaves or shows to the doctor in the course of his detail, is required to have a full disclosure of the effectiveness, side effects, contraindications, warnings, precautions, and so forth, applicable to insure safe, effective use of the drug by that physician—every piece of it.

Senator NELSON. That is the requirement as to advertising.

Mr. GOODRICH. The advertisement requirements differ only in the sense that a brief summary of information related to side effects and contraindications is permitted in general advertising. In direct mailing pieces and other labeling material the discussion must be in greater depth and detail.

Senator NELSON. Well, is it in as much detail as the package insert?

Mr. GOODRICH. Not completely, but it has to be substantially the same—not in the same words, not in the same unattractive form as that you see in the package insert. But the message has to be substantially the same. That is, all of the side effect, precaution, warning, contraindication ideas that are presented in the package insert, must be presented in the mailing piece.

Senator NELSON. And you do review that?

Mr. GOODRICH. To the extent of the facilities available for surveillance, yes.

Senator NELSON. Do you ever find any of this literature that does not comply with your requirements?

Mr. GOODRICH. Yes, we do. And we find that some of it does not comply for many different reasons. We have had instances in which the company claimed that a paragraph was left out inadvertently. It is entirely possible that might have been so. There have been other instances in which the writeup was shortened unduly. There have been instances such as with the Merck Sharp & Dohme here this morning, in which a message that we thought was quite clear, that the drug did cause ulcers, is translated into a lesser language that ulcers have occurred. We find all types of this. The surveillance over prescription drug promotion is a full-time job for an active person—for several active persons who have a great interest in this problem.

Senator NELSON. Dr. Ley?

Dr. LEY. The material which will be presented in subsequent hearings will give the concrete example of a preclearance operation of a promotional ground for the detail man's use in the physician's office. I think this review will answer many of the questions that you are directing at us today as a concrete example.

Senator NELSON. We will leave the rest of the questions on the detail men until subsequent hearings.

Mr. GORDON. As I understand it, then, FDA really does not know what the detail man is saying about Indocin; am I correct?

Senator NELSON. Or any other drug.

Mr. GOODRICH. We know what his company tells him to say. Now, we do not know what he says when he goes to Dr. X's private office and talks with him about the drug. The only way we could know about it is if the doctor tells us. This is a delicate part of surveillance in which we have no mechanism of carrying it forth, except as the doctors tell us.

Mr. GORDON. I believe we have had testimony in the past that the oral presentation is probably the most important presentation of all to the doctor; that the doctor very seldom, if ever, reads the promotional material, printed material, that is left with him; that he relies to a large extent or mostly on the oral presentation.

Now, you will also recall that in the *Love v. Wolf* case, the court held that the activities of the detail men in the case of Chloromycetin washed out the warnings in the printed material. Do you recall that?

Mr. GOODRICH. Yes.

Mr. GORDON. Even if you had adequate staff, and you were to revise your regulations, would this be enough to protect the public?

Mr. GOODRICH. Well, I know that certainly the drug companies feel that detailing is an effective means of promotion. But I could not accept the idea that the tremendous amount of money and effort and the elaborate outlays of printed material have no impact on the prescriber. I think myself that an ad, such as the one you have before you, has a tremendous impact on the doctors prescribing.

Mr. GORDON. I do not say it would not be helpful in protecting the public. But would other measures be necessary. Would this alone be enough?

Mr. GOODRICH. I do not know what you are suggesting, Mr. Gordon. It certainly would be fine with us if doctors who considered the detailing they got was wrong would communicate with us, we would be much interested in that. We would be prepared to take action if we found violations. But that is the only mechanism we have for getting at that, beyond assuring everyone that all the printed material,

all the graphic material, does make a full breast of the whole thing.

Mr. GORDON. But that is a big problem, isn't it?

Mr. GOODRICH. It is one problem, of course.

Mr. GROSSMAN. Mr. Goodrich, on this same point, I assume, then, that you believe physicians read these drug ads in the professional journals. I was just wondering—you said you assumed they had a major impact on doctors. Do we have any evidence—have we had any survey, anything that shows what doctors actually read in this area, and what they believe—or how they are influenced?

Mr. GOODRICH. Dr. McCleery says he has a survey. I base my statement on a quotation from an advertising man himself who made it over in Baltimore at a meeting soon after the law was passed, that we could be sure that if advertisements do not sell drugs, they will not continue to run. And for that reason, I am convinced that they do play a major role.

Mr. GROSSMAN. Has there been any study or survey on this, Dr. McCleery?

Dr. MCCLEERY. Yes, there have been several, and several published. I brought one along today in case we were asked. I think it will reinforce Mr. Goodrich's point concerning the isolated effect of journal advertising alone. By saying that, I would not like to imply that I do not feel there is a general agreement amongst all sides of our dispute, on industry's and our side, that the activities of the detail men constitute the most effective element of all elements of promotion, and as such is a very great and, as Mr. Goodrich says, an uncovered area of our responsibility. But in terms of the evidence that a printed ad is effective in leading to a change in prescribing habits, I will make available copies for the record—from our library. In 1966, we received one of these studies conducted under the sponsorship of Modern Medicine magazine, and conducted by an expert polling outfit, the Politz outfit. What they set out to do, using all of the skills of isolating an area so as to measure effect—and, without going into all the details as to why, it seems that they succeeded. What they did was to take old drugs, eight old drugs—the name of this publication is "The Important Thousand"—done as a Modern Medicine Politz study on advertising effectiveness. We will make copies of it available, but the conclusions are very revealing, I think.

The magazine was interested in determining, for understandable reasons, was what it would be possible to learn—about the effects of ads for some selected drugs, that were not being actively detailed, and had not been for some time, and for which there were no mail campaigns going on, and which had not been going on for some time. They set up a control study to determine the effect of eight ads for eight products, and that is what the basis of this study was.

Now, among the effects and the results they found was that the "belief in excellence" of a product was increased 18 percent by the very simple one or two page black and white or color ads used in this study; and that, as to that most important parameter of effectiveness, the increase in that "intent to prescribe" was of the order of 21 percent. All this from a very small ad, for only six consecutive issues in the Modern Medicine magazine, and in no other journals.

There are numbers of studies like this which show that even the effect of journal advertising alone is quite substantial in leading physicians to change their prescribing habits.

I might point out, in contrast to this very simple, limited advertising on one and two pages for old drugs, that the Merck introductory ad for Indocin in the JAMA (of which you have a copy) in November 1965, was a 10-page, very impressive, four-color ad. It ran for 6 months, approximately. The impact of this kind of ad, in this and many journals, I believe would be likely to be substantially greater than the 21 percent results from these rather limited ads.

Senator NELSON. What study was that?

Dr. McCLEERY. It was an Alfred Politz study for Modern Medicine magazine.

Senator NELSON. Is additional discussion of that going to be presented?

Dr. McCLEERY. I intend, if you wish it, to give you a copy of the entire study.

Senator NELSON. Yes. Do you intend to discuss it further at a future hearing?

Dr. LEY. If the Senator wishes, we may.

Senator NELSON. I would like to see a copy of it, and then appropriate parts of it might be printed in the record. But we ought to have a chance, as Mr. Goodrich says, to evaluate it.

I want to thank all three of you very much. You have made a most valuable contribution to the hearings. We appreciate your taking the time to come here and present this testimony.

(The information submitted by Senator Nelson follows:)

MERCK SHARP & DOHME,  
West Point, Pennsylvania,  
July 14, 1966.

H. I. WEINSTEIN, M.D.

Director, Division of Medical Review.

ACTING CHIEF,

Medical Advertising Branch/DMR.

Indocin (indomethacin)—Misbranding under 502(n).

I. "Indocin" article in July 1966 issue of *Pageant* magazine by Phyllis and Robert P. Goldman.

II. 3-page ad in the July 4, 1966 *Journal of the American Medical Association*.

III. Recommendation.

#### I. PAGEANT ARTICLE, TITLED "INDOCIN"

A. The subject article has come to our attention most prominently in connection with information accompanying a letter of June 21, 1966 from Mr. John E. Fletcher (Merck) to Mr. Cron. This was called to our attention by Mr. Goodrich, who also asked us to check Indocin's medical journal ads. Mr. Fletcher attached a copy of his note of June 17, 1966 to members of the Merck management admitting that the firm cooperated with the Goldmans in making information available for the article, but disclaiming any responsibility of Merck in the matter on the grounds that the article was not "promoted" or "sponsored" by the firm.

B. Thus, the question whether FDA has jurisdiction over the article must be settled before proceeding to deal with the question of whether its contents misbrand the drug.

Even taking Merck's admission and disclaimers into account, we believe that the *Pageant* article is subject to section 502(n) of the Act and that Merck is a responsible party for causing issuance of the article:

1. While section 502(n) excludes labeling defined by regulation 1.105(1), it includes all advertisements and other descriptive printed matter that is not determined to be labeling.

We believe that the *Pageant* article should be regarded as "other descriptive printed matter" that is not labeling.

2. Section 502(n) of the Act does not require material subject to the Act to be "promoted" or "sponsored" by a prescription drug manufacturer, packer or

distributor. It requires only that such material be issued or caused to be issued by the manufacturer, etc.

We think it is clear from the dictionary meanings of "cause" that Merck caused the *Pageant* article to be issued. For example, a pertinent meaning is that "cause applies to any event, circumstance, or condition or any combination of these that brings about or helps bring about a result."

There are several statements in the article that could not possibly have been made unless the information had been furnished by Merck; thus, it is apparent that the firm can be considered to have caused the article to be issued.

Additionally, the article itself contains direct confirmation of Merck's participation in causing the article to be issued. For example, on page 8, the authors state:

" . . . many of them [patients] are moved to sit down and write about their experiences with the drug to its producer, Merck, Sharp and Dohme of West Point, Pennsylvania."

"The following are some samples of these letters to the pharmaceutical firms: . . ."

C. In our opinion, the *Pageant* article by Phyllis and Robert P. Goldman misbrands Indocin, a prescription drug, under section 502(n) of the Act.

Having "caused" the article to be issued, Merck then had the obligation to insist that it meet the requirements of section 502(n). Merck did not meet this obligation. For example, the article fails to contain a true statement of information in brief summary relating to side effects, contraindications and effectiveness as required by section 502(n)(3) and regulations 1.105(e) and 1.105(f)(1).

We believe that a most serious aspect of this misbranding situation is the flagrant appearance of claims in the article that go far beyond the indications for use approved in the package insert. For example, use of Indocin for "bursitis," "trick knee," "tennis elbow," and "a host of other less common disorders characterized by pain and swelling in and around the joints" has not been approved in labeling for the drug. To demonstrate Merck's direct responsibility in causing such unapproved claims to be published in the offending article, the following sample of a letter furnished to the writers by Merck is quoted:

"From Minneapolis: 'Because of bursitis I had to give up golf two years ago. But with your wonderful medicine I'm in good enough shape now to play golf once again . . .'"

## II. THREE-PAGE AD IN THE JULY 4, 1966, JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

### A. Promotional Copy (re effectiveness)

1. The headline, "extends the margin of safety in long-term management of arthritic disorders," is misleading since:

a. It implies that sufficient experience has been obtained to establish Indocin's long-term safety. This is neither the case, nor does the approved package insert (FPL) contain such an affirmation.

b. It contains an implication that Indocin is safer than all other effective anti-arthritic agents for long-term therapy. This is neither proved, nor does the FPL contain such an affirmation.

c. The claim, ". . . of arthritic disorders," is too broad. It extends the FPL indications by implication to other arthritic disorders which have not been approved for inclusion in the FPL. At least it should be modified by a word such as certain."

2. The use of the quote from the Hart and Boardman article (attachment #1), under the caption "rheumatoid arthritis," is misleading since:

a. It is taken out of the context of the article which reveals that the very impressive phrase, ". . . in most cases of active rheumatoid arthritis," refers to the small number of 8 out of a total of 15 cases.

b. It fails to reveal that dosages far in excess of those approved in the FPL were employed (see pages 966 and 968), at least in the early phases of therapy: e.g., 200-300 mg./day versus the FPL's upper initiating limit of 75 mg./day.

c. It fails to reveal, for fair balance, that approximately 60% of the patients with rheumatoid arthritis got side effects, and that all of these got more than one side effect (pp. 969-970).

d. The duration of therapy (p. 966) in these patients was far too short to support the layout's implication that this paper supports the headline's claim of long-term safety.

3. The use of the quote from the Rothermich reference (attachment #2), under the caption "ankylosing spondylitis," is potentially misleading:

a. The quote seems to come from a scientific article. This is not the case—it is from a 2-inch abstract apparently of a talk presented at the "American Rheumatism Association" meeting in 1964.

b. The quote is accurate, but it is surprising that the company used this abstract as a reference when almost certainly the full details have been published as a regular article later in 1964 or early in 1965. (We have not yet located this article.)

c. The use of the abstract is also potentially misleading since long-term results (re the headline's claim for safety) and dosages were not included. Therefore, dosages that produced these results may well have been in excess of FPL limits.

d. For fair balance, against the quote of good results described in the Hart article above, the company could have included Rothermich's results in rheumatoid arthritis. In this same abstract, he stated that although "Excellent results have also been obtained in some cases of rheumatoid arthritis . . . there have been striking failures as well . . ."

4. The use of the quote from Englund, under the caption "degenerative joint disease (osteoarthritis) of the hip," is at least potentially misleading:

a. It gives the appearance of being from an article in a symposium-book. Such are not widely distributed, nor easily available.

b. It was not available in BuMed Library. Dr. Standard of DSB/DMR made a trip to the NIH Library, which had a copy.

c. There was no reference to Dr. Englund's work on page 27, as cited.

d. There was no reference to an article by him in the symposium, either in the index or table of contents.

e. We did locate a physician by that name, in the AMA directory, practicing in Phoenix, Arizona.

f. We will search further to try to find the quote. It could be seriously misleading if Dr. Englund did not, as seems likely, have all "500 patients on indomethacin for about three years" (italic added).

5. The use of the quote from the same Hart and Boardman article (attachment #1), under the caption "gout," is misleading and shows a serious lack of "fair balance."

a. The quote from a seemingly authoritative source from a leading foreign medical journal implies that this opinion must have been based on a large experience (unspecified in quote), and that it was consistent with the general experience of experts using the drug according to the FPL.

b. It was not:

(1) The implied claim that indomethacin is the drug of choice in acute gout is not supported by the FPL.

(2) A reasonable source of early consensus on a relatively new drug, about which "drug of choice" claims are being made, is the view of the AMA Council on Drugs. Its view is expressed in *New Drugs* (1966)—"Because it has produced relief in acute attacks within 48 hours, and because it lacks the untoward effects of colchicine, some clinicians consider it to be the drug of choice for these attacks; however, controlled trials are needed to determine how its effectiveness compares with that of colchicine."

If the company wanted properly to use the authors opinion, it should have included the dosage they used and the number treated. Even then, "fair balance" would still require inclusion of an authoritative opposite or consensus view if such existed.

(3) The experience was not large—the authors report on a study of only 15 cases treated for relatively short periods (see pages 966 and 967).

(4) The "good" results, that led the authors to make the quoted statement, were based on dosages far in excess of permitted (150 mg./day) upper FPL dosage limits—they administered 200–500 mg./day for several days (see pages 966 and 967).

(5) Their opinion was not based on a well-controlled experience. In only 7 patients were any direct comparisons made, and that only to one drug, phenylbutazone (see Table II, page 967). Even here, 3 patients out of 7 preferred phenylbutazone to Indocin.

c. It is very misleading that the company should employ this quote to imply it represents an accepted view of Indocin's effectiveness compared to all other drugs, especially when they know it is based on a very limited (15 patients) and uncontrolled experience—and when the results achieved are based on dosages far

in excess of approved dosages. Both of these important and material factors are concealed from the reader of the ad.

B. *Re: the "Brief Summary"*

The following important warning ideas in the FPL are omitted from the ad's "brief summary":

1. "As with other anti-inflammatory agents, Indocin may mask the signs and symptoms of peptic ulcer." (see Contraindications)

2. "Indocin itself *may cause* peptic ulceration . . ." (see Contraindications)

3. ". . . Indocin *may cause* [single or multiple] ulceration of the stomach, duodenum, or small intestine." (see Precautions and Adverse Reactions)

4. "The possible potentiation of the ulcerogenic effect of these drugs [steroids, salicylates or phenylbutazone] cannot be ruled out at present." (see Precautions and Adverse Reactions)

5. A summary of the following cautionary information (see Precautions and Adverse Reactions):

"Rare reports where it is not known whether the effects can be attributed to the drug include bleeding from the sigmoid colon either from a diverticulum or without a known previous pathologic condition, and perforation of pre-existing sigmoid lesions (diverticulum, carcinoma). In other rare cases a diagnosis of gastritis has been made while Indocin was being given. One patient developed ulcerative colitis and another regional ileitis while receiving Indocin."

### III. RECOMMENDATION

Seizure, with or without such injunctive measures as may be feasible.

When Mr. Goodrich called, he asked that we expedite our review of the ad and article while they are still current. He felt that the two items might be joined in one regulatory action. For this reason, they are both included in this one memo.

R. S. McCLEERY, M.D.

MERCK SHARP & DOHME,  
West Point, Pa., September 22, 1966.

Hon. L. H. FOUNTAIN,  
Chairman, Intergovernmental Relations Subcommittee, Committee on Government Operations, House of Representatives, Washington, D.C.

DEAR MR. FOUNTAIN: This is in reply to your letter of September 7, 1966, enclosing an ad from the August 15, 1966, issue of the Journal of the American Medical Association for Indocin (indomethacin, Merck).

This advertisement and the labeling of the drug have been undergoing review by this agency. In our opinion, the ad is inconsistent with the prescription drug advertising provisions of the law. Further, we regard the quotes from the medical literature used in this ad as not being in conformity with the guidelines described in my statement to your Subcommittee on May 25, 1966.

We are proceeding to take corrective action in this matter.

Sincerely yours,

JAMES L. GODDARD, M.D.,  
Commissioner of Food and Drugs.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,  
October 31, 1966.

FRED BARTENSTEIN, Jr.,  
Administrative Vice President,  
Merck & Co., Inc.,  
Rahway, N.J.

DEAR FRED: This acknowledges your letter of October 26, 1966, about my speech at the PAC in New York City, October 20.

My points were based on a medical evaluation of your Indocin ad. Our Philadelphia District has been instructed to issue citation to your firm. This involves both the Pageant article and the ad. You will, of course, have the opportunity to make your points in response to the citation.

We feel that the effectiveness of the drug and its safety in use have been misstated. The things I pointed out involved the approved brochure (before the recent revision) and the ad which is still running. We do not agree that the "profile" of "Indocin" remains the same today as it appeared when the new drug application was approved.

The revised mailing piece is also under review. It was not approved by us in the form in which it issued. Our impression is that it is more a promotional piece than a warning letter. As to the gout claims, our position is as stated in New Drugs (1966). As to the omitted warning information, please compare the approved brochure with the advertisement.

Very truly yours,

WILLIAM W. GOODRICH,  
Assistant General Counsel, Food and Drug Division.

[U.S. Government Memorandum]

NOVEMBER 2, 1966.

To : Herbert L. Ley, Jr., M.D., Director, Bureau of Medicine. Through : H. I. Weinstein, M.D., Acting Associate Director for Medical Review.  
From : Acting Director, Division of Medical Advertising/OMR.  
Subject: Misleading promotional labeling piece under guise of apparent "Dear Doctor" letter re Indocin.

By first class mail, a letter (copy attached) was sent 10/4/66 by the firm in an envelope flagged for the physician's attention by a beguiling euphemism, "Safety," in very large red letters.

It contained the attached new FPL submitted, under 130.9 (presumably "justified" because it only added warning ideas), by 9/2/66 Company letter to Dr. John Jennings. Whether this was a legitimate act is open to serious question since revision of the FPL was under serious dispute in several details at the last meeting of BuMed and Company personnel on 7/15/66.

The 9/2/66 letter (copy attached) affirmed the intent to put the FPL into use O/A October 31, 1966, without awaiting approval as would be necessary if it were a supplemental NDA submitted under regulation 130.4—this is spite of the fact the 9/2 letter was really a "negotiating" communication turning down a number of specific requests made at the same 7/15/66 meeting.

The above must also be viewed from the perspective that the Company therein rather imperiously turned down at least two important requests for "warnings" by BuMed—see paragraphs "2)" and "3)" of the letter's page 2. Their unwillingness to state, "*NOT FOR USE IN CHILDREN*," appears irresponsible in the face of their knowledge of deaths in children—deaths not prevented by the old FPL language they even here aver to be adequate.

Further, they jumped the implied 10/31/66 "use" date by putting the FPL into use via the 10/4/66 letter to the medical profession.

*Misleading features of subject "October, 1966" letter:* 1. The first sentence sets the tone of the letter as blatantly promotional. It is both out of place and a non-sequitur, since experience in 98 of the 99 countries is largely if not solely beside the point. This is especially improper because of the tie-in to the second sentence's idea that presumably only this massive "global" experience with circa 150 million patient days therapy resulted in the few and new additional warning idea "reflected in the revisions . . ." in the included FPL.

2. The Company's decision to highlight "one change in particular," namely the "potential of masking . . .," must be judged against the following :

a. It represents a unilateral act of rejection of a BuMed proposal to warn of the "Possible activation of latent infection." (See 9/2/66 letter, page 3.)

b. The above "change" constitutes a minimized alert to a standard idea, which, while important, has competed successfully in the Company's "mind" against the prominent inclusion of the following *new* FPL contraindications and side effect ideas:

- (1) Contraindicated in aspirin-sensitive asthmatics and during lactation.
- (2) Convulsion, depersonalization.
- (3) Jaundice, hepatitis.
- (4) Angiitis, elevated blood pressure.
- (5) Acute respiratory distress.
- (6) Agranulocytosis.
- (7) Hyperglycemia.

3. It subtly promotes use of the drug more widely than the FPL permits:  
a. Re: end of first sentence, ". . . in the treatment of *arthritic* disorders . . ."—and the end of the last sentence, ". . . next to aspirin, the most frequently prescribed *antirheumatic* drug . . ." (underscoring added);

(1) Although the "descriptive" first paragraphs of the old and new FPL begin with the latter phrase (notably it is in quotes, "antirheumatic"), and end with "rheumatic disorders," this information refers only to the "generic" capacity of the drug and is clearly not an approved broad indication for such "generic" use of Indocin.

(2) The forced association in the physician's mind with aspirin and its use in rheumatic fever, acute rheumatic arthritis and "carditis," etc., is at least potentially misleading.

*Recommend:* Prompt and vigorous regulatory action, with serious consideration being given to the advisability of a forced "remedial" letter designed to correct the above misconceptions.

R. S. McCLEERY, M.D.

[U.S. Government Memorandum]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,  
FOOD AND DRUG ADMINISTRATION,  
November 4, 1966.

To : Herbert L. Ley, Jr., M.D., Director, Bureau of Medicine.

Through : John J. Jennings, M.D., Acting Associate Director/ODS.

From : Marvin Seife, M.D., Acting Deputy Director/DSR.

Subject : Indocin (indomethacin)—NDA 16-059

A revised indomethacin package insert, #6176404, dated August, 1966, submitted on September 2, 1966, contained most of the changes suggested by the Bureau of Medicine at a meeting with M.S.D. on July 15, 1966. Nevertheless, additional revision of the proposed insert is considered mandatory.

A. A drug warning statement must appear at the beginning of the insert as follows :

**IMPORTANT WARNING**

"Indocin, brand of indomethacin, cannot be considered a simple analgesic and should never be administered casually. Each patient should be carefully evaluated before treatment is started and should remain constantly under the close supervision of the physician. The drug should not be used in children because safe conditions for use have not been established and severe reactions, including fatalities, have been reported."

B. The following misleading words, phrases and unsupported material should be deleted from the package insert introductory section, (paragraphs one and two).

1. Paragraph one, sentence one—omit the word "antirheumatic".
2. Paragraph one, sentence three—eliminate the entire sentence—"Unlike corticosteroids, it has no effect on pituitary or adrenal function.")
3. Paragraph two, sentence one—omit the phrase "of all ages".
4. Paragraph two, sentence two—omit the phrase "in patients with rheumatic disorders".

C. Indications :

1. The first sentence should be changed from "INDOCIN (indomethacin) has been effective in the treatment of:" to "INDOCIN (indomethacin) has been found effective in the symptomatic treatment of".

2. Eliminate the sentence following the listing of the indications: ("In these conditions indomethacin may often replace other commonly used agents such as corticosteroids, salicylates, phenylbutazone—like compounds, and colchicine.")

3. Rheumatoid Arthritis Section: Eliminate the last sentence of paragraph one—"Treatment should be continued for at least a month before concluding that it has not produced significant benefit")—unless M.S.D. can substantiate the recommendation contained therein.

D. Contraindications :

1. Eliminate sentences four and five from paragraph one.
2. The third sentence of paragraph one should be changed from "For these reasons it should not be given to patients with active peptic ulcer, gastritis, or ulcerative colitis, and should be used with caution if there is a history of these disorders." to "For these reasons it should not be given to patients with active peptic ulcer, gastritis, regional enteritis, or ulcerative colitis, and should be used with caution if there is a history of these disorders."

3. The last paragraph of this section must be eliminated in favor of a straightforward statement such as—"This drug should not be used in children because safe indications for use have not been established and severe reactions, including fatalities, have been reported."

E. Dosage and Administration:

1. Paragraph three of this section must be eliminated in favor of a straightforward statement such as—"This drug should not be used in children because safe indications for use have not been established and severe reactions, including fatalities, have been reported."

The issuance of an Indocin (indomethacin) DRUG WARNING letter to the medical profession is necessary in view of the aforementioned package insert additions and changes, the extensive use of this drug, and the possibility of severe and fatal reactions.

[U.S. Government Memorandum]

JUNE 16, 1967.

To: R. S. McCleery, M.D., Acting Director, Division of Medical Advertising/OMR.  
From: D. C. Hurwitz, M.D., Office of Drug Surveillance.  
Subject: Survey of NDA Data by Dr. D. W. Englund.

I have reviewed the Indocin studies conducted by Dr. D. W. Englund contained in Volumes 4, 11, 53 and 76 of the Indocin file. The specific material reviewed consists of two copies of a speech presented before the Merck Research Institute at West Point, Pennsylvania on February 11, 1965, one letter to Merck Sharp and Dohme describing the results of clinical studies, and clinical data on 172 patients.

Dr. Englund has apparently had extensive clinical experience with Indocin, and he discussed in his speech at West Point his experiences with 550 patients using Indomethacin. At the time of this speech, Dr. Englund had been studying Indocin for two years and 50% of his total patient group had been taking the drug for eighteen months or more. Diagnostic categories included rheumatoid arthritis, rheumatoid spondylitis, psoriatic arthritis, gout, scleroderma, lupus, osteoarthritis and primary fibrositis. The author claimed good results in all groups. The largest single diagnostic category was rheumatoid arthritis in which 426 patients were treated with the drug and 362 or 85% showed "definite benefit and clinical improvement." Of 32 patients with rheumatoid spondylitis, 30 showed definite clinical improvement. The percentage improvement varies from group to group but in general the majority of patients were significantly improved.

The only data available to support Dr. Englund's contentions is contained in Volume 11 in which the raw data for 172 patients is assembled. There seems to be a representative cross section of the diseases that he has treated. The treatment period varied from one to "over forty-eight" weeks with the largest number of patients (70) having undergone treatment for 13-24 weeks. Only 22 patients received the drug for longer than 48 weeks at the time the data was compiled—March 13, 1964. Forty patients remained unreported because the investigator did not feel that they had been on the medication for sufficient time to enable evaluation.

As with most of the other Indocin studies the data consists of a clinical evaluation sheet on which various parameters are observed and an overall response to Indocin therapy graded none, poor, fair, good or excellent. In common with the other studies of this type carried out by the company, this clinical trial is completely uncontrolled and lacks the usual elements contained in a well-designed study: a placebo controlled group, random patient selection, regulation of dosage and length of administration of drug, as well as adequate and carefully designed response criteria. The study therefore has testimonial value only and in no way can be construed to show any objective evidence of efficacy of the drug in question. Unfortunately, the author's all-to-obvious bias has undoubtedly played a large role in his evaluation of the efficacy of Indocin.

In conclusion, then, one can regard this study as having only testimonial value in determining the efficacy of Indocin. While such a study has some value for preliminary use in determining whether it is worthwhile to further investigate a compound, it certainly has no definitive value in determining efficacy in this group of diseases since they do not lend themselves to easy clinical evaluation. I am able to find data for only 172 of Dr. Englund's 550 patients; it is impossible to tell at this time whether the rest of the data was submitted in another volume

and has been overlooked or whether it was never submitted to Merck Sharp and Dohme.

JULY 19, 1967.

HOWARD I. WEINSTEIN, M.D.,  
*Acting Associate Director for Medical Review, Med.*

R. S. McCLEERY, M.D.,  
*Acting Director Division of Medical Advertising, OMR.*

126-350 B—Indocin (indomethacin)—  
Alleged Misbranding through Advertising—  
S & R Philadelphia District, January 26, 1967  
and I-AR DCG to Med 2/1/67.

#### SUMMARY STATEMENT

We have reviewed Philadelphia District's S & R dated January 26, 1967 and its attachments, as well as the written response by Attorney Coburn, representing Merck, to charges set forth in Notice of Hearing dated November 23, 1966. In summary, we do not believe that the firm has presented adequate defense in relation to the charges. Taking into account the shipment date (11/7/66) of sample 126-350 B; the fact that the 9/26/66 *JAMA* ad contained changes in the "Brief Summary" that affect the 1.105(f)(1) charges which stemmed from the July 4, 1966 *JAMA* ad (which was the initial basis for our critique of July 14, 1966); more recent information suggesting new or revised charges; etc., we have re-evaluated the situation and conclude that the case should proceed in relation to Indocin advertising. However, the situation now indicates that the FDA should consider dropping the basis for the Notice of Hearing of November 23, 1966, i.e., the Indocin ad in the *JAMA* issue of September 26, 1966, but retaining the sample (126-350 B) as a basis for certain charges in relation to a more suitable Indocin ad.

#### RECOMMENDATIONS

It is recommended that the case be redeveloped in three categories as discussed below and that a new citation be instituted, because it will be noted that the advertisement under this proposal that caused the misbranding is not the same as the one on which the initial citation was based, because the more recent ad is more closely dated in reference to the collected sample, and because the charges have been considerably expanded primarily due to more extensive violative features. Specifically, we recommend that advertisement for Indocin in *The American Journal of Medicine*—November, 1966 be alleged as misbranding the November 7, 1966 shipment of Indocin represented by sample 126-350 B. The package insert accompanying this sample is "Effective: August 1966" and identified in Collection Report of November 18, 1966.

JANUARY 26, 1967.

#### SUMMARY AND RECOMMENDATION

Sample number, 126-350 B; Product, Indocin Capsules, 25 Mg.; Date shipped (on or about), 11-7-66; Carrier, Parcel Post; Seizure, None.

#### CITATION ISSUED TO

Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pennsylvania 19486

#### LEGAL STATUS

The firm, Merck Sharp & Dohme Division, is a wholly owned subsidiary of Merck & Co., Inc., a New Jersey corporation with principal place of business at Rahway, New Jersey.

The officers are as follows: Stuart T. Henshall, President; John J. Horan, Executive Vice President, Marketing; Frederick K. Heath, Vice President, Professional Communications; John L. Huck, Jr., Vice President, Market Planning; Eugene L. Kuryloski, Vice President, Sales.

#### ALLEGED VIOLATIONS

Misbranded by failure of medical journal advertisement sponsored by the manufacturer to fairly show the effectiveness of the drug in conditions for which it is recommended in the advertisement and failure to achieve fair balance in its presentation.

Misbranded by failure of medical journal advertisement sponsored by the manufacturer to contain a true statement in brief summary relating to side effects, contraindications and effectiveness.

#### WITNESSES FOR INSPECTIONAL AND ANALYTICAL FINDINGS

*Sample Collection:* Inspector William M. Troetel (P), 126-350 B, November 18, 1966, DOC. 126-351 B, October 28, 1966.

*Analytical:* Analyst John L. Mietz (P), 126-350 B, DOC. 126-351 B November 23, 1966.

#### RECOMMENDATION

*Prosecution of:* Merck Sharp & Dohme, Division of Merck & Co., Inc. (126-350 B)

#### REASONS FOR RECOMMENDATIONS

##### *Summary and Findings*

The product, Indocin (Indomethacin), is a newly developed nonsteroid drug which was first marketed following the approval of NDA June 10, 1965. The medical journal advertisement for the product appearing in the September 26, 1966 issue of the *JAMA*, is one of the earliest ads for the product. Sample 126-350 B represents a shipment made on November 7, 1966, 11 days after the publication date of the journal. The product was shipped from the firm's West Point, Pennsylvania warehouse to The Drug House, Inc., Trenton, New Jersey, for distribution to retail pharmacists in central New Jersey.

The advertisement was critically reviewed by several members of the Bureau of Medicine and citation issued to the firm for various types of shortcomings:

- (1) The copy for the ad, particularly the headlines employed, utilized broad and unwarranted statements such as "extends the margin of safety in long-term management of arthritic disorders."
- (2) Unwarranted and misleading representations concerning quotations from articles describing clinical studies and failure to quote the unpleasing data from the same articles.
- (3) Lack of fair balance in omitting pertinent information on contraindications.

The firm was cited to a hearing scheduled to be held at Philadelphia District on December 6, 1966. At the request of the respondent firm the hearing was rescheduled for December 14, 1966.

##### *History of Firm*

About 10 years ago, Merck & Co. acquired Sharp & Dohme and incorporated this drug manufacturing firm as a corporate division presently doing business as Merck Sharp & Dohme. Corporate offices are maintained in the manufacturing facility located at Sunneytown Pike, West Point, Pennsylvania. According to our most recent inspections, this firm manufacturers and markets an estimated \$130 million annually in prescription drugs for human use. A review of available files shows no record of formal regulatory action instituted against the West Point firm. A check of New York District records may disclose regulatory actions involving the parent corporation, Merck & Co. Our records indicate the firm has been involved in the recalls enumerated below:

- (1) 10-5-64—Sulfasuxidine, 0.5 Gm.—Carton mixup.
- (2) 10-30-64—Cortone Acetate, 0.5%—Carton mixup.
- (3) 1-14-65—Alflorone Acetate, 0.1%—Below potency.
- (4) 2-9-65—Hydrides Tablets, 25 Mg.—Tablet mixup.
- (5) 4-15-65—Cortisone Acetate Ophthalmic, 2.5%—Carton mixup.
- (6) 5-20-65—Emulsion Mephyton, 10 Mg. and 50 Mg.—Emulsion breakdown.
- (7) 9-22-65—Cathomycin Capsules, 250 Mg.—Penicillin cross-contamination.
- (8) 9-22-65—Cathomycin Lyovae, 500 Mg. Vials—Penicillin cross-contamination.
- (9) 110-10-65—DMSO (in all combinations, concentrations, and package sizes)—All current IND's terminated.
- (10) 12-19-65—Decadron, 0.1% and Decadron-N—Lacks pharmaceutical elegance.
- (11) 2-14-66—MK-665—Firm's IND terminated.
- (12) 5-20-66—Cremomycin, 8 oz.—Lack of expiration date.
- (13) 7-18-66—Tyroderm, 0.5 Mg/gm.—Declared potency.

(14) 11-3-66—Humorsol, 0.25% and 0.125%—Increased incidence of eye irritations.

In addition to the above, the firm recalled eight drug products which had been distributed to outside clinical investigators whose eligibility to handle investigational drugs was terminated. Investigations are presently continuing on the firm's handling of DMSO and MK-665 with view to ascertaining whether or not there is adequate evidence to sustain criminal action concerning the firm's handling of these investigational drugs. With the exception of the Humorsol recall, all of the recalls are considered "closed" from the standpoint of adequate accounting for the returned merchandise.

#### RESPONSIBILITY FOR ALLEGED VIOLATIONS

Our investigations of the promotional practices of the larger pharmaceutical firms indicate the planning, drafting and approval of medical journal advertising involve essentially an institutional decision on the part of the firm. In addition, outside advertising agencies are generally involved. In the instant case we do not believe we have evidence to fix any individual responsibility for the placing of this ad beyond the responsibility normally carried by corporate officers. For this reason, we have not recommended the naming of individual defendants.

#### INTERSTATE RECORDS AND LABELING

The records covering this shipment consist of invoice issued by Merck Sharp & Dolme and identified by both dealer's statement and affidavit of the consignee firm. In addition, we have established distribution of the medical journal and prescribing of the product through affidavit of Mischa F. Grossman, M.D., Cherry Hill Hospital, Cherry Hill, New Jersey, whose affidavit states that he has received the September 26, 1966 issue of *JAMA* which bears an advertisement for Indocin, and that in the regular course of his practice he has prescribed Indocin for some of his patients.

#### RESPONDENTS' VIEWS PRESENTED AT HEARING

At the hearing held on December 14, 1966, the firm was represented by house counsel Robert L. Banse and retained counsel Hayward H. Coburn of Drinker Biddle & Heath, Philadelphia, Pennsylvania. At the hearing the firm indicated that it would challenge the validity of regulations, disagree with our conclusions and question the wisdom of recommending prosecution for this type of violation. The respondents stressed, however, that the firm's actual response would be in the form of a detailed written response and asked that our evaluation be based on the written record. They did submit a tabulation (Exhibit A) but indicated this would be resubmitted with their written response. During the hearing X asked to be provided with a copy of Dr. England's article in the *Excerpta Medica Foundation* because our medical officers had been unable to locate this publication. They promised to furnish me a copy, but stressed again this would be done apart from their response in that our Charge Sheet had contained no allegations concerning this publication. At the insistence of the respondents for adequate time to prepare their response, they were granted until January 10, 1967 to present this material.

The firm's response to the charges is set forth in considerable detail in Exhibit B and will not be repeated here because the response, itself, should be studied in view of this proposed action. Briefly, the firm challenges our legal position concerning our jurisdiction over false and misleading statements in the body of the advertisement. The firm disagrees with our conclusions concerning use of terms such as "extends the margin of safety in long-term management of arthritic disorders." The firm sets forth its disagreement with each of the interpretations we have alleged in the Charge Sheet. The firm contends that the quotations from the articles cited below the illustrations in the advertisement fairly represent the views of the author. The firm takes issue with our views on listing of contraindications in the brief summary and claims its condensation is both fair and accurate. The firm's views are supported with a tabulation comparing information alleged to be omitted with information actually presented in the advertisement.

The firm also advances the view that even if it were in error the circumstances do not merit institution of criminal action. It recites the history of its dealings with General Counsel William W. Goodrich, Commissioner James L. Goddard

and representatives of the Bureau of Medicine. The firm takes the position that since it has made forthright correction of the alleged violations prosecution should not ensue. Attached to the firm's response is a copy of the advertisement for the November 14, 1966 issue of *JAMA* which it contends fully meets the requirements of Section 502(n).

#### DISTRICT'S CONCLUSIONS

In reviewing the firm's position in response to the hearing we find we cannot agree with most of the firm's contentions. With regard to the jurisdictional question concerning false and misleading claims in the body of the advertisement, we understand this was one of the issues presented by the industry during its initial request for a hearing on the proposed regulations. Thereafter, in the ensuing dialogue the industry withdrew its objections in light of the exchange of memoranda of understanding. Although we do not have a record of these events at the District, we understand that Merck Sharp & Dohme was a party to these proceedings and its attack upon the validity of the regulation is somewhat belated.

We believe the misrepresentations concerning the comparative safety of Indocin are serious in nature, particularly in light of the continued receipt of medical data indicating this product must be prescribed with caution. The manner in which the clinical studies were quoted is also of serious consequence, particularly when viewed from the standpoint that few physicians have available to them the original articles to compare for a more complete evaluation of the product. In this connection, we wish to point out that one of the articles (the *Excerpta Medica Foundation* booklet) could not be located in our rather extensive medical library.

The firm's comment concerning references in the brief summary to ulceration of the stomach, duodenum, or small intestine, may have some merit. If this recommendation is approved, I believe it would be well to delete reference to them lest we become involved in unnecessarily complex semantics in presentation of our case.

Although the firm presents persuasive arguments for mitigating circumstances tending to establish that need for prosecution no longer exists, we do not agree with the firm's position. As one of the leaders of the pharmaceutical industry, the firm had available to it the best brains and talent in the medical advertising field, yet it chose to utilize advertising tactics that should have been abandoned upon passage of the Kefauver-Harris Amendment of 1962. The contention that mitigating circumstances can exist appears to be of little consequence when we consider there exists no adequate method to correct the improper advertising once it has been printed and disseminated to prescribing physicians.

#### SPECIAL REVIEW REQUESTED

In separate communication of January 10, 1967 (Exhibit C), Mr. Coburn transmitted a copy of the *Excerpta Medica Foundation* publication entitled "NON-STEROIDAL ANTI-INFLAMMATORY DRUG THERAPY IN RHEUMATIC DISEASE" (Exhibit D). Attached with the Summary and Recommendation is the single copy of this publication which the Bureau of Medicine requested for review. Upon review of this material they may consider inclusion of additional charges. If they do, we recommend no additional citation issue because the charges would be included within the general scope of the first portion of our Charge Sheet enclosed with the Notice of Hearing.

IRWIN B. BERICII,  
Director, Philadelphia District.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,  
FOOD AND DRUG ADMINISTRATION,  
Philadelphia Pa., January 3, 1968.

MERCK SHARP & DOHME,  
Division of Merck & Co., Inc.,  
West Point, Pa:

Investigation by this Administration indicates your responsibility for violation of the Federal Food, Drug, and Cosmetic Act, as described in the attached Charge Sheet, with respect to the following:

Consignment of an article labeled in part: (btl) "100 \*\*\* CAPSULES INDOCIN (INDOMETHACIN) \*\*\* 25 mg. Merck Sharp & Dohme West Point, Pa. Division

of Merck & Co., Inc. CAUTION: Federal law \*\*\* H30SS" shipped by you on or about November 7, 1966 to The Drug House Inc., 1880 Princeton Avenue, Trenton, New Jersey.

An informal hearing will be held on Monday, January 15, 1968 at 10:00 (EST) in Room 1204 U.S. Customhouse, 2d and Chestnut Streets, Philadelphia, Pennsylvania, to give you an opportunity to present your views in the matter. The enclosed INFORMATION SHEET explains the purpose and nature of the hearing, and how you may reply. If no response is received on or before the date set, our decision on whether to refer the matter to the Department of Justice for prosecution will be based on the evidence at hand.

By direction of the Secretary of the Department of Health, Education, and Welfare.

IRWIN B. BERCH,  
*Director, Philadelphia District.*

#### PROHIBITED ACT

Section 301(a) of the Federal Food, Drug, and Cosmetic Act. The introduction or delivery for introduction into interstate commerce of any food, drug, device, or cosmetic that is adulterated or misbranded.

#### CHARGES

A. The journal advertisement for Indocin appearing in the November 1966 issue of the *American Journal of Medicine* causes the drug to be misbranded under section 502(n) of the Act in that said ad does not fairly show the effectiveness of the drug in the conditions for which it is recommended in the advertisement and fails to achieve fair balance in its presentation as required by regulation 1.105(e) in that:

1. The headline "Extends the margin of safety in the long-term management of arthritic disorders" misleadingly implies that Indocin is safer than all other effective anti-arthritic agents for long-term therapy. Furthermore, the unqualified phrase "arthritic disorders" misleadingly extends by implication the indications for use in the labeling accepted as part of the new drug application.

2. The quotation ". . . the first non-corticosteroid agent which produced a predictable and measurable reduction in joint-swelling in most cases of active rheumatoid arthritis" from an article by Hart and Boardman (Hart, F. D. and Boardman, P. L.: *British Medical Journal*, 2:965, October 19, 1963) under the ad caption "rheumatoid arthritis" does not represent a true statement of effectiveness for Indocin and presents a distorted view of the drug's effectiveness. In addition, the use of this quotation, along with the reference to the October 19, 1963 article by Hart and Boardman is further misleading in that the quotation and reference is obsolete since it fails to take into account a more recent and more scientific article by the same authors.

3. The quotation "Indomethacin is the drug of choice in acute gout. . ." attributed to Hart and Boardman (Hart, F. D. and Boardman, P. L.: *British Medical Journal*, 2:965, October 19, 1963) appearing under the caption "Gout" misleadingly implies that the author's opinion was based upon a large experience and that it was consistent with the general experience of experts using the drug according to the approved labeling. Furthermore, the claim "the drug of choice" for this new drug, is not supported by the NDA and is contrary to all expert opinion.

4. The quotation "I have had some 500 patients on Indomethacin now for about 3 years. I find it an extremely helpful drug. I think there are certain areas where it will be without question the drug of choice. One of these is osteoarthritis of the hip" attributed to Englund (Englund, D. W. in *Non-Steroidal Anti-Inflammatory Drug Therapy in Rheumatic Disease*, New York Excerpta Medica Foundation, 1965, page 27) appearing under the caption "degenerative joint disease (osteoarthritis) of the hip" is misleading in that the statement "I have had some 500 patients on Indomethacin now for about 3 years . . ." when considered in relation to the headline claim, "extends the margin of safety in the long-term management of arthritic disorders" misleading gives the reader the impression of powerful support through massive research experience of 3-years-long administration to 500 patients on a new drug, when in fact, the statement is an "off the cuff" remark at a symposium supported by a grant from Merck, Sharp & Dohme.

In addition, the advertisement fails to achieve fair balance in that the advertisement failed to give the reader a more properly balanced view of this new drug by not including the summary view, expressed by the moderator at the end of the symposium, that Indocin's use ". . . warrants a lot more study and observation. Its long-term effect in rheumatoid arthritis is still unknown. . . ."

B. The article is misbranded within the meaning of 502(n) in that the journal advertising failed to present information concerning those side effects and contraindications that are pertinent with respect to the uses recommended or suggested in the advertisement as required by regulation 1.105(f)(1) in that the following important information has been omitted:

1. The warning that "as with other anti-inflammatory agents, Indocin may mask the signs and symptoms of peptic ulcer."

2. The warning that "indomethacin itself may cause peptic ulceration or irritation of the gastrointestinal tract."

3. The contraindication that "indomethacin is contraindicated in aspirin-sensitive asthmatics."

4. The precaution that "indomethacin should be used with caution if there is a history of ulcer, gastritis, regional ileitis, or ulcerative colitis, because of its potential for causing gastrointestinal bleeding."

5. The precaution that "It [indomethacin] may cause simple or multiple ulceration of the stomach, duodenum, or small intestine."

6. The precaution that "a possible potentiation of the ulcerogenic effect of these drugs cannot be ruled out at present."

7. The side effect information concerning "ulceration of the esophagus, convulsions, nausea, anorexia, vomiting, epigastric distress, abdominal pain, diarrhea, gastritis, jaundice, hepatitis, elevation of blood pressure, hematuria, angioneurotic edema, angitis, rashes, loss of hair, acute respiratory distress including dyspnea and asthma, purpura, thrombocytopenia, agranulocytosis, hearing disturbances, orbital or pariorbital pain, vaginal bleeding, hyperglycemia, and glycosuria."

C. The article is misbranded within the meaning of 502(n) in that the journal advertisement does not prominently display the name of at least one specific dosage form and quantitative ingredient information in direct conjunction with such display as required by regulation 1.105(d)(2).

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FEBRUARY 14, 1968.

From: R110.  
To: R100—Mr. Barnard.  
Subject: 126-350B Indocin—Merck Sharp & Dohme.

#### SUMMARY

Attached is Philadelphia District's S&R of 2-6-68, renewing their recommendation of prosecution in this advertising case.

Merck's response to the Notice of Hearing is a written response by the Law firm of Drinker Biddle & Reath. The response presents legal, administrative and medical arguments against forwarding.

This matter was the subject of a conference between BRC, Med & GC last October. (See Memo of Conf. 10-16-67, cy. attached.)

Your guidance in this matter will be appreciated.

Bureau of Medicine has not reviewed the Merck's response to this most recent citation.

D. W. JOHNSON.

PHILADELPHIA DISTRICT,  
*February 6, 1968.*

#### SUMMARY AND RECOMMENDATION

#### SUPPLEMENTAL

Sample number, 126-350 B ; product, Indocin Capsules, 25 Mg. ; Date shipped (On or about), 11-7-66 ; Carrier, Parcel Post ; Seizure, None. (This hearing involved additional citation on the sample which was the subject of Summary and Recommendation submitted on January 26, 1967.)

This hearing was held to afford the respondent an opportunity to present his views on additional advertisement appearing in *American Journal of Medicine*, November 1966.

The position of the firm with respect to the charges remains essentially the same. Our review of the written summation does not change any of our views as set forth in the January 26, 1967 Summary and Recommendation. Accordingly, we renew our recommendation for prosecution of Merck Sharp and Dohme, Division of Merck & Co., Inc., on this number.

IRWIN B. BERCH,  
Director, Philadelphia District.

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FOOD AND DRUG ADMINISTRATION,  
*Philadelphia District, February 6, 1968.*

#### RECORD OF HEARING

Sample number and product: 126-350 B, Indocin Capsules, 25 Mg.  
Firm cited [additional citation]: Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pennsylvania 19486.

Date of Hearing: February 6, 1968.

Where Held: Philadelphia District—FDA.

Present: Mr. Hayward H. Coburn, Attorney-at-Law, Drinker Biddle & Reath, Philadelphia, Pennsylvania 19107. Mr. Irwin B. Berch, Director, Philadelphia District.

This hearing was originally scheduled for January 15, 1968 and was rescheduled at the request of the respondent. Mr. Coburn presented an up-to-date Legal Status Sheet and acknowledged that the shipment was made as alleged and that the advertisement in question did appear as set forth in the Charge Sheet.

Mr. Coburn stated that the firm's response would be the written response presented to me at the hearing. This is an 18-page statement to which are attached Exhibits A-1, A-2, B, C, D, E, and F. I asked Mr. Coburn whether or not the firm had made any changes in its promotional or advertising practices since the receipt of the current citation. He stated the firm's revisions are reflected in the mailing to physicians (Exhibit E) and the revised advertisement (Exhibit F) which appeared following the earlier citation. He added that, in common with other newly-introduced drugs, additional data accumulated from human experience serve to identify other possible human reactions. He assured me these were being regularly incorporated in the revised labeling which the firm submits in accordance with the new drug regulations.

The respondent did not remain for the dictation of this hearing record.

IRWIN B. BERCH,  
Director, Philadelphia District.

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MERCK SHARP & DOHME,  
*West Point, Pa., March 8, 1968.*

DIRECTOR

*Bureau of Medicine*

ACTING DIRECTOR

*Division of Medical Advertising/OMS*

We concur in the prosecution recommendation of Philadelphia District in its S & R dated February 6, 1968, and we recommend that the subject number not be placed in permanent abeyance unless such action is advocated in an opinion from General Counsel. We think that there is a valid basis for prosecution on the issues. Further, the attitude of the firm, as reflected in the letter response to the Notice of Hearing dated January 3, 1968, is poor to the extent of inviting prosecution notwithstanding its *pro forma* conclusion that prosecution should no follow.

Our comments will be directed to the written response dated February 6, 1968 and prepared by H. H. Coburn, attorney for Merck on the staff of Drinker, Biddle and Reath. Our purpose will be to show: (a) the poor attitude of the firm, (b) the inadequacy of the response, and (c) to point up tryable issues that we believe exist on the basis of the clear language of the statute, and apart from the regulations. Our comments are not intended to be all-inclusive.

## A. ATTITUDE OF THE FIRM

The poor attitude of Merck regarding the advertising regulations has persisted since their promulgation. This is clearly shown in the following passage from attorney Coburn's letter:

"Regulations 1.105(a)-(e) to the extent they purport to regulate or specify the contents or form of an advertisement for a prescription drug in other respect [except as provided in the statutory language of section 502(n)] are, we submit, unauthorized by law and do not constitute an independent basis for determination of whether or not a violation of Section 502(n) has occurred."

In effect, Merck challenges all of the principles of fair balance provided in the existing regulations, and even challenges the Government's authority in respect to requiring ingredient information in advertisements except as specified in 502(n).

We believe that Merck's challenges present a basis for trying the validity of the promulgated-regulations 1.105(a) through (e). Because revisions of the regulations are in process, however, the time may not be advantageous to the Government to proceed toward a Federal Court determination of the validity of the existing regulations, particularly 1.105(e). We are omitting, for the present, comments in rebuttal of Merck's position in respect to the charges on the promotional copy of the ad. We have to say, however, that the Merck position in respect to each of the charges against the promotional message is, in our view, extremely weak should such issues come to trial. We would anticipate reframing charges in relation to the promotional message within the statutory language.

## B. EXAMPLES OF ISSUES AVAILABLE UNDER SECTION 502(n) RELATING TO OMISSIONS

1. The statute provides that the advertisement alleged to misbrand the sample must include a true statement of information in brief summary relating to side effects and contraindications.

(a) A charge was that the ad omitted the warning (side effect) information that "As with other anti-inflammatory agents, INDOCIN may mask the signs and symptoms of peptic ulcer."

The respondent implies evasively and erroneously that the contraindication in the ad applying to "active peptic ulcer" satisfied the test of a true statement in relation to the quoted side effect.

The issue is whether that side effect information is in brief summary or otherwise in the ad. We contend that it is not.

(b) A charge was that the ad omitted the warning (side effect) information that "indomethacin itself may cause peptic ulceration or irritation of the gastrointestinal tract."

The respondent claims that the information "is clearly set forth in the advertisement." The claim is untrue.

The issue is whether any information in the ad meets the tests of a true statement with respect to the quoted side effect. We contend that it does not.

A charge was that the ad omitted the precaution (relative contraindication) that "a possible potentiation of the ulcerogenic effect of these drugs [steroids, salicylates, phenylbutazone] cannot be ruled out at present."

The respondent does not deny the omission but uses somewhat unintelligible language to reconcile the omission by stating that the omission "strengthened the specific warning against *any* use of INDOCIN in the presence of the conditions stated, with or without other agents."

The issue is whether the quoted precaution is omitted from the ad. We contend that it is.

(d) A charge was that the ad omitted side effect information concerning a list of specific side effects which included, among others:

(1) nausea, anorexia, vomiting, epigastric distress, abdominal pain, diarrhea, gastritis; and

(2) angioneurotic edema, rashes, acute respiratory distress, purpura, thrombocytopenia.

The respondent does not deny the specific omissions but attempts to reconcile the omissions by stating that the side effects (1) were included under the "general side effect of 'G.I. disturbances'" and that the side effects (2) were included under the "general side effect of 'hypersensitivity reactions'."

The issue is whether the general headings used by the respondent represent a true statement of information regarding the specifically named side effects.

We contend that the test of a true statement has not been met through use of general headings.

2. A charge was that the ad misbranded the sample under 502(n) because it did not prominently display the name of at least one specific dosage form and quantitative ingredient information in direct conjunction with such display as required by regulation 1.105(d)(2).

The respondent attempts to defend the charge (1) by making a general denial of the validity of the regulation and (2) by implying irrationally that regulation 1.105(d)(2) is dependent on 1.105(d)(1). The fact is that 1.105(d)(2) is an independent regulation, as a careful reading will disclose.

Consistent with not proceeding toward Federal Court determination of the validity of existing advertising regulations now under revision, we do not believe that regulation 1.105(d)(2) is needed as a basis for continuing the essential element of this charge.

Section 502(n)(2) provides the basis for requiring "the formula showing quantitatively each ingredient of such drug to the extent required for labels under section 502(e)."

Possibly due to ignorance, the respondent appears to take comfort in relying on section 502(n)(2) as a basis for omitting quantitative ingredient information from the ad. He even goes so far as to recite the language of 502(e) to require "the label to bear . . . in case it is fabricated from two or more ingredients, the name and quantity of each active ingredient."

The fact is that Indocin Capsules, 25 mg., are fabricated from 2 or more ingredients; this means that the quantity of indomethacin (the active ingredient) in the capsule must be declared on the label and in the advertisement.

The issue here is so clear cut that it needs no further comment.

#### C. COMMENTS ON CERTAIN FEATURES OF THE RESPONDENTS LETTER OF FEBRUARY 6, 1968

1. The respondent claims that the contraindication that "indomethacin is contraindicated in aspirin-sensitive asthmatics" was included in labeling for the first time in a package circular put into general use on October 31, 1966. It claims, therefore, that it was not possible to make the change in this advertisement on such short notice. In this connection, the respondent states in paragraph 7 on page 13 of its letter, in relation to a separate charge of omitting a large number of specific side effects from the ad, that such side effects were only included in the labeling at the same time as the foregoing contraindication.

The respondent also claims that the period of 90 days (suggested as a guide by Dr. McCleery on January 23, 1968) for conforming promotional labeling and advertising to package labeling had not expired when the ad appeared.

It can be shown that the respondent is in error in respect to the claims regarding the timing involved.

2. Section D of the respondent's letter deals primarily with matters such as meetings between the Agency and Merck management; current more careful handling of clearances within the firm; voluntary destruction of substantial quantities of promotional material, presumably also violative; a prior citation; the fact that a prosecution would be punitive [which is admitted], etc.

We believe that such information as that presented by the respondent to show good behavior would be properly the subject of an inquiry from a probation officer. Such information is often useful in determining the amount of fine, etc. This was the case when Wallace Laboratories was prosecuted in re Pree-MT; in that case Wallace not only had undertaken massive corrective action but also took Pree-MT off the market.

We believe that the prosecution action taken against Wallace should be taken into account in determining whether Merck should be prosecuted in relation to this sample.

R. S. McCLEERY, M.D.

MARCH 11, 1968.

DIRECTOR, BUREAU OF REGULATORY COMPLIANCE.

DIRECTOR, BUREAU OF MEDICINE.

The Bureau of Medicine recommends that prosecution of the firm be instituted, subject to approval by General Counsel. As you may note from the attached memorandum of March 8, 1968, subject as above, from the Division of Medical

Advertising to the Bureau Director, specific comments are provided in response to the communication from the firm on February 6, 1968. We will be pleased to discuss the matter with you and the General Counsel at any time.

HERBERT L. LEY, Jr., M.D.

Senator NELSON. Dr. Norman Rothermich, who conducted a trial with Indocin, has just returned from Europe. He has requested the opportunity to present a statement to the committee.

We will recess until 1:30.

(Whereupon, at 12:35 p.m., the subcommittee was recessed, to reconvene at 1:30 p.m., on the same day.)

#### AFTERNOON SESSION

Senator NELSON. Dr. Rothermich, I apologize for being late, but I was tied up and, until this moment, I could not get here.

The committee is pleased to have you appear before us today. We are well aware of your distinguished professional credentials. Did you submit a biographical sketch with your statement?

#### **STATEMENT OF DR. NORMAN O. ROTHERMICH, CLINICAL PROFESSOR OF MEDICINE, OHIO STATE UNIVERSITY; SENIOR PHYSICIAN, COLUMBUS MEDICAL CENTER; MEDICAL DIRECTOR, COLUMBUS MEDICAL CENTER RESEARCH FOUNDATION, COLUMBUS, OHIO**

Dr. ROTHERMICH. No; I did not, Senator.

Senator NELSON. Would you wish for the record to simply give your professional credentials and background?

Dr. ROTHERMICH. Either that, or I can save time by sending you it in writing—

Senator NELSON. If you would prefer to do that for purposes of accuracy, we would be glad to print prior to your statement your biographical and professional background.

Dr. ROTHERMICH. I will send you a complete biography.

Senator NELSON. Thank you, Doctor.

(A subsequent biographical sketch was received and follows:)

#### BIOGRAPHY OF NORMAN O. ROTHERMICH, M.D.

Born: October 9, 1912: St. Louis, Mo.

St. Louis University: B.S. 1934; M.D. 1936 (also special postgraduate student in biochemistry under Dr. E. A. Doisy, 1933-36).

1936 to 1940: Internship at St. Louis City Hospital; residency at Robert Koch Hospital in St. Louis and at Ohio State University and Columbus State Hospital.

1941: Appointed Chief of Arthritis Clinic at Ohio State University Hospital.

1942 to 1946: Military service; Army Medical Corps, Southwest Pacific Theater (special certificate, Army School of Roentgenology).

1946: Certified, American Board of Internal Medicine.

1950: Fellow, American College of Physicians.

1947 to 1959: Founder and Director, Division of Rheumatic Diseases at Ohio State University College of Medicine.

1947: Post graduate study in Rheumatology at The Mayo Clinic.

1948 to 1950: American College of Physicians postgraduate courses in Internal Medicine at the Universities of Michigan, Pennsylvania, Northwestern, Harvard and Duke University.

1941 to Present: Faculty, Ohio State University College of Medicine, Full Professor of Clinical Medicine 1960.

1957: President, Columbus Academy of Medicine.

1955: Founder and Director of The Columbus Medical Center Clinic and Research Foundation.

1952: Founder and Director of the Arthritis Foundation, Central Ohio Chapter. Author of more than forty publications in endocrinology and rheumatology, complete bibliography upon request.

Member, American Rheumatism Association and six other national medical scientific organizations.

**Senator NELSON.** If there is any part that you wish to extemporize on or summarize, you may do so. In any event, your full statement will be printed in the record.

**Dr. ROTHERMICH.** Thank you.

First, Senator Nelson, I would like to express my gratitude for your accommodating me. I know this is at some trouble. I am appreciative of it.

**Senator NELSON.** We are glad to do so.

**Dr. ROTHERMICH.** I did not have an opportunity to see the testimony of Dr. O'Brien and Dr. Mainland until, I think, Monday night. So this has been prepared since that time. I have reviewed it once and corrected it, but it is not as detailed as I would like it to be. However, I am satisfied that it carries my position and I think it will help to clarify it and I would like to read it.

**Senator NELSON.** Because you wrote it so hurriedly, if there is something you recollect subsequently that you would like to add to your statement, send it to the committee and we will include it with your statement.<sup>1</sup>

**Dr. ROTHERMICH.** Thank you, sir.

I would like to say at the start that in requesting the privilege of making this statement for the hearing records, it is not my wish to subject you to a medical backyard brawl. I would like to make clear that I carry no ill will nor any personal animosity toward Dr. Mainland or Dr. O'Brien, who appeared before you last week. My work on indomethacin needs no defense or apology, and I assume that my reports in the medical literature are not on trial. I do believe that Dr. O'Brien made some unwarranted statements which, though assuredly unintentional, cast reflection on my professional integrity and competency. I should like to reply to those statements and perhaps offer additional comments which may help to clarify for you some points, both in my reports and elsewhere, which apparently have not been entirely understood.

Without intending any impertinence, I feel compelled also to offer a mild demurrer that the committee did not find it appropriate or desirable to invite me to appear before it, despite the acknowledged major influence of my reports in the Journal of the American Medical Association.

I am not a statistician and know little of the ways of such, but, as I will try to illustrate later on, it would seem that, contrary to a rather generally held impression, statistics is not an exact science. Furthermore, I am not a laboratory or test tube doctor, although I have a degree of experience with laboratory and animal experimentation. I am generally regarded, and consider myself to be, a clinical rheumatologist, engaged primarily in the medical examination and treatment of people. I am a full professor of clinical medicine at Ohio State

<sup>1</sup> See supplemental statement beginning at p. 3276, *infra*.

University College of Medicine on a part-time basis, and for this I receive a small annual salary. The major part of my time is engaged in private medical practice in a group association with other internists. All income derived from the application of my medical knowledge is received by me as a percentage from my share of the partnership receipts.

A large proportion of my private patients suffer from various rheumatic diseases, and I am particularly interested in the problem of rheumatoid arthritis, which in my opinion is one of the most devastating, persistent, and painful diseases which affect mankind. Rheumatoid arthritis is a major producer of disability, striking characteristically in the most productive years. The degree of this disability has not been entirely recognized by business and industry, for reasons not clear to me. Rheumatoid arthritis is not one of the so-called glamour diseases and has not received the attention it deserves from the public nor, I am afraid, from some segments of the medical profession, and in certain aspects it might be said to have an "untouchable" status. Patients with rheumatoid arthritis seem to sense this general attitude and feel almost apologetic or embarrassed at having their disease. The disability aspect is all too apparent, and the patient makes every effort to adjust to and compensate for disability. However, the constant and relentless nature of the pain and suffering are little appreciated and not well understood.

Now, I would like the opportunity to reply to certain of Dr. O'Brien's statements which I thought were unwarranted. On page 4528, he refers to my publication in the Journal of the American Medical Association, volume 195, page 1102, May 1966 (although he fails to refer to the equally important paper published 1 month prior in the Journal of the American Medical Association, February 14, 1966, page 531). He states that the study is highly biased, but I must insist it was done without bias and with complete objectivity. He makes objection to my statement "placebo was introduced whenever the patient seemed to be established and well controlled on indomethacin therapy."

MR. GORDON. Doctor, may I interrupt you for a moment?

My feeling when I heard Dr. O'Brien testify was that when he used the word "bias," he used the word "bias" from a statistical point of view. I do not know, but it certainly did not seem to me that he used it in an ad hominem sense.

SENATOR NELSON. I do believe that he did not intend to say that you, yourself, were biased. I think that is correct.

DR. ROTHERMICH. I think he should have made that clear in his statement. He should have said it was statistically biased, because he refers later to a statistical bias, so I assume this statement that "it was biased" meant that it was personally biased.

SENATOR NELSON. I do not have the understanding that he intended that, and I do not think he would intend to imply that you were personally biased. I think he was talking about statistics and I think that you may have interpreted it in a way he did not intend.

DR. ROTHERMICH. Basing this exception on the fact that the disease is "cyclical," he introduces a non sequitur in his reasoning when he states that "since the disease is cyclical, introducing a placebo when a patient was doing well would probably be followed by a relapse."

There is just no connection between those two phrases. If the disease is cyclical, it would be difficult if not impossible to have a patient established and well controlled on indomethacin or any other therapy.

On the contrary, if any disease is under good control by an effective therapy, the introduction of a placebo would probably result in a relapse. Parallel examples of this could be demonstrated by the introduction of placebo in patients with congestive heart failure who are well controlled on digitalis therapy, patients with diabetes who are well controlled on insulin therapy, and patients with thyroid deficiency who are well controlled on thyroid therapy. Clinicians know that in such instances severe relapse would consistently follow each placebo trial. Applying the term "cyclical" to rheumatoid arthritis would suggest a lack of actual clinical experience with the disease. It is true that the disease is characterized in some degree by exacerbations and remissions, but these are highly capricious, both in onset and duration, and do not have any rhythmic circular aspects as suggested by the word "cyclical." A patient with rheumatoid arthritis may have an exacerbation with continuing activity of the disease for a year or two or more, and then he may suddenly develop a remission, that is, disease inactivity, for a variable period lasting a month, several months, or in a rare case, permanently. Exacerbations are much more protracted and tenacious, and remissions are usually brief and seldom total. Furthermore, even if the disease were cyclical, the introduction of a placebo would certainly not "probably be followed by a relapse." The introduction of a placebo relapse when the disease was apparently well controlled by a certain drug is evidence itself that the drug was actually controlling the disease, and this is reinforced when relapse is precipitated on more than one occasion by the repeated introduction of placebo.

**Mr. GORDON.** Doctor, I have here an article from Clinical Pharmacology and Therapeutics, by Drs. Albert M. Katz, Carl M. Pearson, and Joseph N. Kennedy.<sup>1</sup> I should like to read something from it:

All eight subjects who received the drug (with benefit) followed by placebo experienced severe exacerbations within 24 hours of the change. One patient had a severe exacerbation lasting four days, after he was symptomatically the same as when taking indomethacin. Once again, he was given the drug, but derived no further benefit. The experience in this case cast some doubt upon the validity of accepting an exacerbation which occurs after a drug has been discontinued or replaced by a placebo as proof of the drug's efficacy.

Would you comment on that?

**Dr. ROTHERMICHL.** I would agree that one case does not prove anything.

**Mr. GORDON.** He talks about eight subjects.

**Dr. ROTHERMICHL.** He only mentions the one case, though, as an exception to that.

**Mr. GORDON.** Yes, and his conclusion is that the experience in this case casts some doubt upon the validity of accepting an exacerbation which occurs after a drug has been discontinued or replaced by a placebo as proof of the drug's efficacy.

**Dr. ROTHERMICHL.** Do you not yourself think that one case out of eight is rather a weak statement?

<sup>1</sup> See p. 3277, *infra*.

Mr. GORDON. I am not a doctor. I am just giving you the conclusions reached by a team of doctors.

Dr. ROTHERMICHI. I am asking you as a layman, not a doctor. One case in eight. Do you think that proves anything at all, really?

Mr. GORDON. You do not agree with these people?

Dr. ROTHERMICHI. I think it has no significance at all.

Mr. GORDON. There is no significance?

Dr. ROTHERMICHI. One out of eight, no.

On page 4528, Dr. O'Brien states that "a study of this type was designed in such a way that the bias is in favor of the drug." This is a highly arbitrary statement, but Dr. O'Brien proceeds to use this as a false premise for further condemning my report. As a matter of fact, the study was not designed in such a way that the bias was in favor of the drug, and I have done other studies in exactly the same manner before and since Indocin, and my conclusions were discouraging and unfavorable to the drug under study.

Mr. GORDON. Have these been published?

Dr. ROTHERMICHI. No, sir.

Mr. GORDON. Have these been given to the FDA?

Dr. ROTHERMICHI. Yes, sir.

Mr. GORDON. Yesterday?

Dr. ROTHERMICHI. No, I said yes, sir.

Mr. GORDON. Could you supply them to us for the record?

Dr. ROTHERMICHI. I think the FDA has all the material I have given them.

Mr. GORDON. I have looked through the files and I have not seen the studies.

Dr. ROTHERMICHI. This is not related to Indocin. This is other drugs.

Mr. GORDON. Oh, you said before and since—

Dr. ROTHERMICHI. Yes, I have done this same kind of study on other drugs and they did not come out at all.

Mr. GORDON. I see.

Dr. ROTHERMICHI. On page 4529, Dr. O'Brien states that my study, as submitted to the FDA, differs drastically from the manuscript that was published in the Journal of the American Medical Association. This would imply that something about this condemns my report. I would like to say that much of this was due to the fact that the editor considered my manuscript entirely too long and felt that he could not devote that much space to it. We had considerable correspondence, between the editor and myself, but I agreed only to delete the word "blind" because of differences with the statistician-reviewer of the journal. It was the opinion of the latter that the blind and double-blind trial could not be done with Indocin, only because of my thoroughly honest statement that "occasionally patients would suspect the placebo substitution by a change in side effects;" and, in reference to and in deference to the statistician-reviewer, I made the further statement in the journal that "for this reason, from the statistician's viewpoint, the placebo trials in this report (and probably in most clinical drug reports) cannot be considered as true 'blind studies'." My article goes on further to elucidate this point, and I should like to quote the sentences which follow immediately after that:

Usually there was enough delay in this awareness (of a change in side effects) to permit the therapeutic assessment. Furthermore, the appearances of side effects are often capricious and inconsistent, thus further limiting the patient's ability to detect placebo.

I went on to state:

The placebo substitutions were made in 86 of the patients, and in 70 of these there was a decisive clinical relapse on placebo. This clinical relapse was verified on repeated placebo trials in 55 patients.

In my opinion, these are well controlled observations, despite the fact that some statisticians would deny the validity of "single-blind" trials.

I believe it should be emphasized right at this point that, if the statistician reviewing my manuscript for the Journal of the American Medical Association was of the opinion that the appearance of side effects from indomethacin invalidated any single- or double-blind trials, logic and consistency would demand that he deny the validity of the double-blind trials carried out by Dr. Mainland and his group, and other double-blind trials. Apparently, what is one statistician's meat is another statistician's poison. There is not consistency.

When Dr. O'Brien implied that it was demeaning of me and my report that it was published in "modified form," he is not being entirely fair to this committee. The fact is that medical journal editors are generally assuming more and more of an authoritarian position and demanding modification of practically every article or report submitted to them. These modifications are based on recommendations from editorial boards and reviewers who no doubt are themselves quite human and fallible. And I might add at this point that Dr. O'Brien admitted in his own testimony last week that the article he submitted to Clinical Pharmacology and Therapeutics, to Dr. Modell and three reviewers, was found to contain errors. It was sent back to him, and he had to revise and modify those, so his report was also published in a modified form.

Because of the increasing influence of the statistician in medical reporting, the double-blind trial has been given a position of infallibility which is not entirely justified. For example, does Dr. O'Brien realize that patients will sometimes break open a capsule and taste the drugs to see if there is a difference? If they are taking a capsule one week and getting another one next week and getting a different effect, they may break open the capsule to see if there is a difference. These are difficult things to control when you are dealing with human beings. When you are dealing with animals, it is different. Even though the capsules may look identical, does he realize that some patients will reduce the dose or discontinue the drug if it is giving adverse reactions, but without informing the investigator? I think this is true especially if the work is being done in a large impersonal institutional clinic rather than the atmosphere of close rapport of the personal patient-physician relationship.

This frailty of the double-blind trial is further illustrated in the report of Dr. Mainland for the Cooperating Clinics Committee of the American Rheumatism Association. I should like to add here for the benefit of the committee that this impressive and high-sounding title gives this committee and its work an aura of authority and Olympian omniscience which its own members would be the first to deny categorically and emphatically.

In the first place, with reference to Dr. Mainland's work, it is an extremely attractive hypothesis that a lumping together of observations by a number of different clinics would, because of increasing size

of the sample, increase the statistical validity. The weakness of this is the known remarkable variation between one observer and another. We in our own group, and there are three of us engaged in rheumatology in our group—have tested this repeatedly; and although we have tried on many occasions to standardize our observations and have seen patients jointly and in conference, we still find a distressing degree of variation between the three of us who work so closely and harmoniously as a unit. To have 11 different observers from 11 widely scattered clinics making observations which are then stated to be of an identical character seems hazardous at least. There were a number of exclusions in the ARA-CCC study which would certainly weaken the trial's validity.

For example, the patients were to be "out-patients or domiciliary hospital patients," but it does not say how much of each sample comprised the total. Certainly a rheumatoid arthritic in a domiciliary hospital environment is much more likely to have a quiescent disease than one in an outpatient environment. The exclusion of all patients who have had antirheumatic therapy would effectively eliminate all cases of even moderate severity. So you would have to assume that most of the cases in that study were cases of mild degree.

Senator NELSON. I have a question in reference to your sentence that a rheumatoid arthritic in a domiciliary hospital environment is much more likely to have a quiescent disease than one in an outpatient environment. In setting up a double-blind test, or any kind of study, if those making the study were comparing the person in a domiciliary facility versus one who is outside of it, it would be a fault in the study immediately, would it not?

Dr. ROTHERMICH. Oh, yes.

Senator NELSON. In other words, do you not, in setting up studies, compare age groups and try to get them as comparable as possible?

Dr. ROTHERMICH. Yes, and this factor, Senator Nelson, of putting an arthritic at rest, not necessarily bed rest, but outside of an environment that is distressing to him, putting him away in a domiciliary hospital environment, you see, is much more likely to allow his disease to become quiescent. So they should have said "we have  $\alpha$  number of patients who are hospital domiciliary type and we have  $\alpha$  number of patients who are outpatients," and given the result of those studies in the given categories.

Senator NELSON. In other words, you would compare domiciliary patients versus other domiciliary patients and the outpatients versus other outpatients?

Dr. ROTHERMICH. Yes. I would like to add the point, too, that this study was being done by 11 different centers, and they have, I think, 110 total patients. I think half or more of the centers had less than 10 patients in their study group, and some of them as few as four patients. Now, Dr. O'Brien made the statement before this committee at another point that some of the reports in the literature were only of 10 patients or so and any work on such a small number—I cannot think of his exact words, but the substance of it was that it was meaningless, or had no validity.

Now, he was referring to other types of work. But I would point out to you, Senator Nelson, that the components of this combined study, you see, had less than 10 patients in many of their centers.

Now, I would like to emphasize that not only do they have less than 10 in many of these, but their duration of therapy was only for a few weeks—3 months, which in my opinion is much too short a time to evaluate any drug. This is what I will try to emphasize later on.

They allowed an unlimited consumption of aspirin in both the placebo and the treated patient. So they have no idea of how many aspirin tablets were taken by either group. Now, it is entirely conceivable that a patient may have been on the active drug and taking two aspirin tablets a day, or four aspirin tablets a day, and when placed on placebo, because of an increase of symptoms, he may have increased his aspirin consumption to 12 or 16 a day, but they do not know this.

Senator NELSON. There is no way to be sure about it, is what you are saying?

Dr. ROTHERMICHL. They kept no records of it.

Senator NELSON. Oh, I see.

Dr. ROTHERMICHL. I would like to emphasize, too, Senator Nelson, that I am not saying that this is not a worthwhile trial. I do not mean that at all. I think this kind of trial should be done. But I think it is wrong to assume that this particular type of study is the only study that should be done, and I think it is wrong to assume that this type of study has no flaws. It has many flaws, because we are dealing with human beings. When you can take mice and rats and put them in cages and keep them under fixed control, then you can have the ideal, well controlled study. But when you are dealing with human beings, this is something else again.

Senator NELSON. This has always been my view. I have always said politics would be a wonderful thing if you did not have to deal with human beings.

Dr. ROTHERMICHL. Yes.

I did think it was rather significant that Dr. Mainland himself testified that if he were treating rheumatoid arthritis—although he disclaimed that he was treating any patients—he would select indomethacin for a cautious trial in those patients who have failed to respond to basic therapy, including salicylates, despite the fact that his report indicated negative results.

In this context, for the information of this committee, I would like to quote from my article in the JAMA in the section under comments:

However, it should not be inferred that indomethacin replaces or eliminates the need for a sound basic therapeutic program for the patient with rheumatoid arthritis which should include increased rest, salicylates, physical therapy, and other adjunctive or supportive measures. The patient with rheumatoid arthritis who is not responsive to the basic program of therapy may have this supplemented by the cautious prescribing of indomethacin beginning with a dose, et cetera, et cetera.

It would seem that Dr. Mainland and I have identical views on the clinical usefulness of indomethacin.

In my early studies, I was repeatedly admonished by my preceptors that it was unhealthy for medicine generally and unwise for the investigator to rush into publication with short-term observations. For this reason, I went to great pains to delay my report in the Journal of the American Medical Association until I had accumulated more than three and one-half years of intensive experience with this drug. I subjected the drug to the most thorough and penetrating clinical scrutiny.

Every possible means was taken to determine the true action of this drug and to avoid bias on the part of myself or the patient.

Dr. O'Brien suggests that my patients were badly neglected and that I had lost interest in them until I suddenly presented them with a wonder drug. All of my patients with rheumatoid arthritis continually receive the most personalized attention from me, regardless of what drugs or therapies I have been or am employing. No change whatsoever was made in our approach or routine management. As I have previously stated, most of these patients have at various times been subjected to one or another type of clinical experimentation. In accordance with my own scruples and ethics, and with the law, I did explain to each patient that he was undertaking a new experiment, and often this was done in the presence of a spouse or a near relative, and the patient was then required to sign an appropriate release form.

Dr. O'Brien would lead you to think that some poor miserable arthritic had staggered into my examining room, discouraged and depressed by my indifference to his disease activity, and that I suddenly burst into the examining room, wildly elated and exclaiming to the patient that I had found a wonder drug and that the patient was about to be miraculously cured. Such an ugly implication is dangerous at worst and naive at best.

The fact is that our whole setup was geared to achieve the greatest objectivity in our evaluation of this drug. Of course, as stated previously, I informed the patient fully that an experimental drug trial was to be initiated, but that no patient should feel in any way coerced into joining in this trial, because I think that a patient must give informed consent. I think if there was any bias in our study, it was as a result of this informed consent of the patient, which tended to eliminate the timid and the weak of heart, but this is now required by law and a necessary part of any drug trial.

Under such circumstances, the subjective response of the patient, in my opinion, is about equally divided between some 20 percent on the one hand who want very much to have a good result and therefore get an unrealistic benefit from the drug, and about 20 percent on the other end of the spectrum who, because of their great fear of the nature of experimentation, would like to have the drug discontinued as soon as possible and tend to report minor or imagined ill-effects, or even tend to minimize possible good effects. Only long-term trial with these patients can effectively bring their results into true perspective. Achieving this true perspective can be greatly aided and solidified by the liberal use of placebos, both single-blind and double-blind, as well as by the gradual but systematic reduction or withdrawal of other effective therapies, most notably the corticosteroids, or cortisone.

Likewise, evaluation of side effects of a drug can only be determined in patients on the basis of long-term observation. These side effects must be carefully appraised, keeping in mind at all times the safety of the patient, but weighing and balancing out as far as possible the need for truth and knowledge about the nature of the drug under investigation. In my opinion, it is wrong to suddenly thrust at a patient a double-blind study without some prior preliminary trial of the drug. Such an early double-blind trial is bound to have the built-in problem of the patient's first experiences with the good and

bad effects of a drug, and these will undoubtedly color his own responses to the investigator's questionnaire. In my opinion, such a study is far more valuable if the patient is allowed to be on the drug for a sufficient time to familiarize himself with it and to become casual and unconcerned, and then the application of either single-blind or double-blind studies will have much greater validity.

Finally, I would like to add here—and I do not want Dr. O'Brien to take any offense at this statement, but I must say it—that many rheumatologists would disagree vigorously with his seemingly cavalier statement that no therapy influences the course of the disease. Furthermore, such a statement could have an extremely demoralizing effect on hundreds of thousands of rheumatoid arthritics throughout this country and the world.

The evaluation of rheumatoid arthritis is extremely difficult in all its aspects. Even the diagnosis is often a tenuous one. Our methods of measuring good effects and bad effects leaves much to be desired, and I am sure Dr. Mainland would be the first to agree; in fact, I think he has already reported elsewhere this general opinion about evaluating therapy in rheumatoid arthritis. Parenthetically, I can say that we sat on a panel discussion with several noted rheumatologists in Japan—Dr. Joseph Hollander from Philadelphia and Dr. William Kuzell from San Francisco. This was organized by the Japanese as a panel for evaluating therapy in rheumatoid arthritis. Dr. Kuzell was asked his opinion, and he said the best way to measure it was to say to the patient: How do you feel?

Dr. Hollander went to the trouble of describing a palpometer, which is a mechanical device for squeezing on a patient's joint to see at what point it would cause pain. Now, one of the criteria that the Mainland group used was tenderness of a joint. Now, this is tenderness in San Francisco and in New York and in Miami and so on, and each examiner is squeezing that joint. You cannot make me believe that the one in Miami knows how hard the one in New York is squeezing a joint, too, so that there can be real objective comparison of tenderness.

If Dr. Hollander feels the need to develop a palpometer, I think you can readily appreciate that determining with any exactitude the tenderness of a joint is a very difficult thing.

We have great difficulty in knowing truly how much, if any, influence we have produced on any given disease, and this is about equally true of rheumatoid arthritis, or perhaps a little more so. One could probably say that insulin has no influence on the basic course of diabetes, and there would be a certain amount of truth in this. But no one would say, do not give the diabetic insulin.

How can we say that a patient who has active inflammatory disease in his joints has not had his basic disease altered when the inflammation has been reduced or eliminated by certain types of therapy?

Dr. O'Brien even referred to cortisone as having a powerful anti-arthritis effect. Now, "antiarthritis" means that it acts against inflammation within the joint. If he thinks that cortisone can abolish the inflammation in the joint, he must concede that this has to have some basic influence on the course of the disease.

Even if the eventual outcome of the disease has not been influenced, we still cannot say that it has not been retarded, or its harmful effects minimized or reduced. I think that today you do not see the extremely

severe, advanced crippling of the arthritic that we used to see 20 years ago. I think this is eloquent testimony itself that our therapies are effective in at least partially influencing the course of the disease. We have patients under our care whose disease we regard as static, but whenever we attempt to reduce or withdraw certain therapies, the disease process flares up and accelerates intensively. No single therapy benefits every patient with rheumatoid arthritis, not even aspirin, and, yes, not even corticosteroids. Certainly it has never been suggested, hinted, or implied that indomethacin benefits every case of rheumatoid arthritis.

Senator NELSON. Are there any statistics as to longevity of rheumatoid arthritics now vis-a-vis 20 years ago?

Dr. ROTHERMICHH. I do not believe so. I think that this is a very difficult thing, because of its long term nature.

Senator NELSON. No statistics?

Dr. ROTHERMICHH. Yes, it is very difficult, because patients with rheumatoid arthritis do tend to live an awfully long time; in fact, you might say in some cases too long because of their prolonged suffering. But—to compare longevity—I do not think this has been done.

Finally, the members of this subcommittee should know that eminent, highly competent, and highly respected rheumatologists from all over the world have reported favorably on their results with indomethacin in rheumatoid arthritis and have indicated the important adjunctive place of this drug in its overall management. Numerous congresses on rheumatic diseases have been conducted in various parts of the world, and these eminent rheumatologists (who are held in highest esteem and often closely affiliated with the American Rheumatism Association) in paper after paper have reported favorable results in what they consider to be controlled trials of the drug for extended periods of time.

Most rheumatologists would be dismayed (and large numbers of patients with rheumatoid arthritis would be bitterly disappointed) if they were to be deprived of the clinical and therapeutic benefits of indomethacin on the basis of a few brief-trial negative reports.

I wish to thank you, Senator Nelson, and all of the members of the subcommittee for the opportunity of presenting this statement and having it included in the hearing records.

If I can be of any further assistance or service to the subcommittee, I shall be glad to cooperate as fully as possible.

Senator NELSON. Doctor, we were very pleased to have you come to present your informed viewpoint based upon your long experience.

Mr. GORDON. Dr. Rothermich, I have several letters here written by you to the Merck Co. which were secured from the files of the Food and Drug Administration. I would like to read one of them. This is from you to Merck Co. It says:

Few improvements were noted in the peripheral arthritis group at dosage levels of 150 mg daily. Most of the peripheral arthritics are now being carried on a daily dose of 300 mg daily, but a significant number were benefited to a striking degree to 200 mg daily. The greatest deterrent to increasing dosage to an effective level is the appearance of cerebral toxicity. This manifests itself clinically in excruciatingly severe headaches, dizziness, lightheadedness, disturbances of sensorium, a feeling that the head is floating away or even separating from the body, feeling of detachment from reality. The higher the dose, the more severe the symptoms.

Here you say that most of your patients—these are your words—most—are being carried on dosage of 300 mg. On the other hand, the upper limit of approved dosage is 200 mg. Now, it seems to me that no doctor could repeat your experiences.

In other words, what I am questioning is can your studies be used as proof of efficacy for this drug?

Dr. ROTHERMICHL. What is the date of that letter, sir?

Mr. GORDON. Your letter is dated June 12, 1963.

Dr. ROTHERMICHL. This is the point I have made in my report to the JAMA. On long-term trials, we came to realize that patients experienced cerebral side effects worst when they suddenly had the drug thrust on them in high dosage, and we realized that there were certain times of day when they were more likely to have cerebral side effects than others. We also came to realize that if we began at a very low dose and built it up, they were far less likely to have any significant cerebral side effects.

Mr. GORDON. But you still cannot go over 200 mg. now. That is the approved dosage. You cannot go above that, but you went beyond it in your trial. You went up to 300 mg. and 400 mg., too.

My point is this: The studies that you made cannot be used as proof of efficacy of that drug, because nobody can duplicate that dosage today.

Dr. ROTHERMICHL. No, I said that in my report to the Journal of the American Medical Association, too.

Mr. GORDON. Yes, I know that.

Dr. ROTHERMICHL. That the dosage I used should not be used clinically and therefore physicians could not expect as high a degree of improvement as I had reported—this is stated in that article.

Mr. GORDON. I have it right here.

Dr. ROTHERMICHL. You will see it right in the first part, if the synopsis, right at the bottom, that they should not use this high a dosage, that if they used it in smaller dosage and gradually increased it to tolerance, they would then begin to get effects which were not discernible at the early stages. This was proven repeatedly to us by patients, both on single-blind and on what we call double-blind study, although the statistician for the JAMA refused to allow us to use that term. We felt it was inadequate. But we did feel, as we developed greater experience with the drug, we came to realize that there was a significant number of patients who were getting benefit from indomethacin.

Now, what we were trying to show in our studies, and this was for the benefit of the profession, we felt obligated to report to them as fully as possible. We were trying to show what the maximum dosages were and what would happen if those maximum dosages were exceeded. We put six patients in the hospital, at the university, and subjected them to enormous single-dose trials, as much as 350 milligrams in one dose in the morning, and we made intensive studies on them throughout the day, using all kinds of parameters of study, because we felt we had to know what happened to a human with increasing dosage and where therapy was jeopardized by toxic effects.

Now, we were impressed early in our studies by the cerebral side effects, and I emphasized this: that since then we have learned that we can mitigate or minimize by certain techniques of therapy, by

always giving the drug on a full stomach or with milk at bedtime, as we had recommended in the JAMA report; that we avoid a morning dose; and that we avoid having the patient take it in association with caffeine ingestion, because we feel this aggravates the tendency for the cerebral side effects.

We also did learn that there is a certain idiosyncratic reaction, that some patients are exquisitely sensitive to this. I had one patient develop this in very bad form on 25 mg., whereas many patients can take much more and get no side effects.

Did I answer your question?

Mr. GORDON. Not exactly.

Dr. ROTHERMICHI. Well, what do you want me to say?

Mr. GORDON. You are aware that 200 mg. is the maximum dosage approved by the FDA? That we can agree on.

Dr. ROTHERMICHI. Yes.

Mr. GORDON. You also stated that most of your patients were on 300 mg., which was above the Food and Drug Administration limit, and that it cannot be duplicated today.

Then I asked you whether this could be used as proof of efficacy, given the present limitation by the Food and Drug Administration on dosage. I do not think I got a clear answer from you.

Dr. ROTHERMICHI. I thought I answered quite clearly. I said that we got a remarkably high percentage of good and excellent results, but that in many of these cases the dose was at levels in excess of what should be used in general practice, and that physicians could not expect a comparable high percentage of good effects because they would necessarily have to use smaller doses.

Mr. GORDON. Let me read another excerpt from one of your letters. This is a letter from you to Merek & Co., dated October 12, 1963, in which you state:

Indocin has an excellent beneficial effect in some cases of peripheral rheumatoid arthritis but only a good effect in a large percentage and there is a complete failure or ineffectiveness in a distressingly high percentage of such cases.

Does that add to what you said before?

Dr. ROTHERMICHI. No, I think it simply amplifies it. I think, yes, I would say today that indomethacin will prove of significant clinical—because of the statistician, I have to avoid the word “significant”—that it will prove to be of appreciable clinical benefit, worthwhile for the physician to give his patient, in something over 50 percent of the patients—about 50 or 55 to 60 percent, in that area, on the limited dosages we have.

Mr. GORDON. This is Indocin as against nothing. How about Indocin as against aspirin?

Dr. ROTHERMICHI. Now, I think this brings out a point that I appreciate. Many physicians around the land have a sort of all-or-none attitude toward treatment of rheumatoid arthritis. They give the patient this drug and if it is not beneficial, they stop it, and then they give him that drug. We do not believe in this, and I have said in other papers that combinations of therapy are vastly important in rheumatoid arthritis—that aspirin will contribute, let us say, 10- to 15-percent benefit; Indocin may add another 20-percent benefit; small doses of a corticosteroid may add another 30-percent benefit. Even giving paren-

teral injections of gold may add another. So that the cumulative benefit from small amounts of all of these drugs will give the patient a 70- or 80-percent total benefit.

Do you see? Did I answer that?

Mr. GORDON. Yes.

Mr. Chairman, I ask that this correspondence as well as Part 2 of Dr. Rothermich's article which appeared in the March 28, 1966 issue of *JAMA* be placed in the record right after the testimony of Dr. Rothermich. The chart appearing on page 126 of the 1966 *JAMA* article indicates that most of the patients were on daily doses well above the permitted level.<sup>1</sup>

Dr. ROTHERMICHI. Senator Nelson, I am not objecting that it be put in there, but I believe that the date should certainly be emphasized: 1963 was a long time ago.

Senator NELSON. I don't know if it is particularly relevant at this stage, because that was before we had much clinical experience with it, right?

Dr. ROTHERMICHI. Right.

Mr. GROSSMAN. Doctor, I would like to ask you one question. On page 6 of your testimony, concerning your report in modified form, you say, in the first full paragraph:

The fact is that Medical Journal editors are generally assuming more and more of an authoritarian position and demanding modification of practically every article or report submitted to them. These modifications are based on recommendations from editorial boards and reviewers who, no doubt, are themselves quite human and fallible.

How do you see your role? You talked before about doing things for the benefit of the profession. What do you see as your role in seeing to it that, for example, reports are not published in modified form? If they say they are only going to publish it in a modified form, why would you not say, then, do not publish it if you are going to leave out significant aspects of it? Do you not have some responsibility there?

Dr. ROTHERMICHI. This is a question that I find difficult to answer. I cannot quite agree with the increasing authoritarian position assumed by medical journal editors, and I find that at times they are extremely arbitrary. But, you see, they have total power of veto; and if you want to get some information to the profession, you may find it necessary to modify to some extent.

Now, if you feel it is going to be modified substantially, then I think you are honorbound not to agree to its publication. But when I agreed to the publication by striking out the word "blind," I did go to great lengths to explain in the article for the benefit of the statistician-reviewer, that I was doing this, so I felt that my position was tenable.

Does that answer your question?

Mr. GROSSMAN. I think so. As far as you are concerned, there is no control over the various journals to see that this is not done, except for the particular physician who writes the article. Otherwise, nobody checks to see what he leaves out or what he does not?

Dr. ROTHERMICHI. No, I think when the article is submitted to the medical journal, the editor submits it to several different reviewers. These reviewers may be all academicians, for example, who are not patient oriented and know little or nothing about the practice of

<sup>1</sup> See information beginning at p. 3282, infra.

medicine. They may be laboratory-oriented physicians or they may be statisticians.

I once submitted to the editor of *Arthritis and Rheumatism* an article dealing with my extensive study of the incidence and prevalence of rheumatoid arthritis in criminal and insane populations. We examined 20,000 insane and 4,400 criminals in the Ohio penitentiary to determine if they had rheumatoid arthritis. I submitted this and was told that this was referred to some prison psychiatrist, and he took exception to certain parts of it and wanted to have these deleted. I refused, and the article was not published.

The editor subsequently apologized to me and said that he was bound to follow the reports of his reviewers and his editorial board. He subsequently agreed that he would publish it as a brief report without any editorial changing of it. I had to condense it, then, so that it would fit in length with the qualifications of "brief reports."

**Mr. GROSSMAN.** My point is only this: It seems there should be two responsibilities. One rests with the individual author of the piece, to make sure that his piece is honorable, that it goes to the points, and does not leave anything out; and secondly, that these medical journal editors, whoever they are—I happen to know that we are giving them, if they are nonprofit organizations certain tax advantages and other advantages—these editors should at least own up to these things and make sure we are getting the full story.

**Dr. ROTHERMICHA.** I am sure that these medical journal editors are highly conscientious men, and they strongly believe, some of them, for example, in the infallibility of the double-blind study, which I have today tried to show you is not infallible.

**Mr. GROSSMAN.** Then we are wholly dependent on the individual author's integrity. It comes to a point where he says, I will not let you print my material.

**Dr. ROTHERMICHA.** Yes. Then he might just as well go hide in a closet.

**Mr. GROSSMAN.** He may have to.

**Dr. ROTHERMICHA.** You see, this is the problem now.

**Mr. GROSSMAN.** Thank you.

**Senator NELSON.** Thank you, Dr. Rothermich, for coming in today. We appreciate having you here.

**Dr. ROTHERMICHA.** Thank you.

(A supplemental statement was subsequently submitted by Dr. Rothermich and follows:)

#### SUPPLEMENT TO STATEMENT OF NORMAN O. ROTHERMICHA, M.D.

Finally, I should leave with the committee a clear-cut, concise statement of my present views and attitudes regarding indomethacin, and to emphasize the objectivity of this (as not something suddenly thought up for the benefit of this committee). I will simply quote from the invitational lecture which I gave before 1,200 Yugoslavian doctors at their Symposium on Rheumatic Diseases in Ljubljana, Yugoslavia on Friday, April 26, 1968.

"*Conclusions.*—After six and one-half years of clinical experiences, I continue to regard indomethacin as a valuable adjunct to the treatment of rheumatoid arthritis. It may be considered as a treatment of choice in ankylosing spondylitis, chronic gouty polyarthritis and psoriatic arthritis and may be beneficial in some other miscellaneous rheumatic diseases, such as osteoarthritis (especially of the hip) and in some cases of fibrositis. Cerebral and gastric side effects are certainly not uncommon, but with prophylactic attention to dosage and method of administration and with reasonable vigilance on the part of both the physician

and patient, these should not prove harmful or a deterrent to clinical trial with the drug. As with all drugs, certain peculiar idiosyncratic effects may be expected, but only rarely. No one should make the mistake of thinking that indomethacin is the final word or the cureall for rheumatoid arthritis, but to many of these unfortunate patients it is a godsend and the physician should be prepared to offer such patients this possible benefit. At the same time, he should certainly not ignore the basic fundamental approach to the treatment of rheumatoid arthritis with increased rest, physical therapy, aspirin or other salicylates and attention to any other diseases and malfunctions in the body which may be contributing to or worsening the arthritis."

Lastly, I should also offer to Senator Nelson and the subcommittee my own recommendations regarding the development of a new drug in the field of rheumatic diseases, as follows:

1. Thorough and intensive basic pharmacologic studies in animals and preliminary trials in paid human volunteers.
2. Cautious initiation of therapeutic trials in patients by one or a few experienced clinical rheumatologists, beginning with very low doses and gradually increasing to therapeutic levels.
3. After achieving a satisfactory baseline, the rheumatologist should then introduce single-blind trials with placebos and also initiate attempts at reducing other therapies or eliminate them entirely, if possible.
4. If the drug seems promising from these preliminary investigations (which should last from six months to a year), then controlled double-blind cross-over trials should be initiated by those already studying the drug and also by other qualified groups who may be interested.

5. If these studies continue to indicate promise of therapeutic effectiveness of the drug, then it should be given to a large number of rheumatologists for controlled therapeutic trials over a prolonged period. Again at least six months to a year.

6. If at the end of these studies the drug shows continued therapeutic effectiveness and the side-effects can be considered reasonably acceptable and not unduly hazardous to the patient, the drug can then be released for sale and general prescription by the medical profession.

It is my opinion that the public is well protected by the surveillance presently exercised by the Federal Food and Drug Administration in the development of clinical drug trials. It is not within my province to make any comment regarding drug advertising.

(The supplemental information submitted by Mr. Gordon follows:)

[From Clinical Pharmacology and Therapeutics, vol. 6, No. 1, June 5, 1964, pp. 25-30]

#### A CLINICAL TRIAL OF INDOMETHACIN IN RHEUMATOID ARTHRITIS\*

(Indomethacin, a new nonsteroidal compound, was tested as an antirheumatic drug in 97 patients. Beneficial effects were recorded as excellent in 6, good in 23, and fair in 12. The drug was discontinued in 60 patients, and 3 others were lost to follow-up. The most common reason for discontinuation of the drug was gastrointestinal effects.<sup>1</sup> Peptic ulcer developed in 6 patients.)

(By Albert M. Katz, M.D., Carl M. Pearson, M.D., and Joseph M. Kennedy, M.D., Los Angeles, Calif., Division of Rheumatology, Department of Medicine, U.C.L.A. School of the Health Sciences, and the Wadsworth Hospital, Veterans' Administration Center.)

Indomethacin (Indocin) is a nonsteroidal compound, 1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid, which possesses significant antipyretic properties and analgesic effects in animals.<sup>11</sup> Toxicologic studies in animals showed effects which were similar to those demonstrated by many other anti-inflammatory agents. These included fluid retention, gastric irritation, and ulcerative lesions of the gastrointestinal tract.<sup>3-10</sup>

Since indomethacin is active when given orally, and because it possessed certain potentially advantageous clinical properties, its value as an antirheumatic agent was tested in man.

\*Received for publication, June 5, 1964.

NOTE.—Numbered footnotes at end of article, p. 3282.

## TESTING PROCEDURES

The majority of patients included in this series had one of the rheumatic diseases, in most cases rheumatoid arthritis. Criteria for admission included:

1. Continuing difficulty with current regimen of treatment or the need for large doses of corticosteroids.
2. The ability of the patient to return frequently to the clinic, at least 2 consecutive weeks originally.
3. Freedom from significant complicating disease.
4. A reasonable measure of reliability of the patient's observations of his symptoms.
5. Stage III of ARA classification (although a few stages II or IV are included)\* if rheumatoid arthritis was present.

The patients were first examined weekly, then biweekly, and later monthly. Evaluation was made of the amount of pain, tenderness, effusion, range of motion of the joints or other structures involved, general well-being, the presence or absence of fever, and possible side effects.

Almost all patients were on other medications at the time indomethacin was first administered. Medications were continued at the same dose level so as not to influence the evaluation of the effect of the indomethacin. In some cases, however, the dose of other drugs, such as cortisone, was reduced when the indomethacin was found to be of benefit. Some patients were evaluated in a study in which they received either indomethacin or an identically appearing placebo. After one week on one treatment, the drug was changed without the patient's knowledge to the opposite substance.

The dosage of indomethacin ranged from 100 mg. to 400 mg. daily, given in the form of 25 or 50 mg. coated tablets in the most convenient divided dose schedule for the patient. Four hundred milligrams was given as 100 mg. four times each day, 300 mg. as 100 mg. three times daily, etc. In the beginning, patients were instructed to take the medication with meals but, as gastrointestinal side effects became evident, they were instructed to take it after meals. Antacids were used prophylactically in a number of subjects in the later phases of the study. Periodic laboratory examinations, which included complete blood count, erythrocytic sedimentation rate, urinalysis, stool guaiac, serum bilirubin, alkaline phosphatase, serum glutamic oxaloacetic transaminase (SGOT), and serum uric acid, were performed. Other examinations were made as indicated.

The test drug was immediately discontinued if any potentially serious complications developed, or if annoying side effects became more incapacitating than the disease under treatment. If no benefit was noted after a suitable period of time, usually about 2 weeks, the trial was concluded. Each patient was seen by one of the three authors. Every patient started on the drug is included in this report: 97 in all, 52 females and 45 males. Age ranges from 10 to 81, with the majority between 30 and 50.

## RESULTS

The effects of indomethacin on clinical signs and symptoms were rated by comparison with the therapeutic regimen of aspirin that nearly all of the patients had been receiving immediately prior to the trial. The major benefit was a decrease in joint and muscular pain and stiffness. A significant number of patients also experienced a marked decrease in the duration and intensity of morning gel, or the elimination of it altogether. The response was considered *fair* if it was judged to be as effective as a therapeutic amount of aspirin, *good* if it greatly surpassed aspirin, and *excellent* if it completely relieved symptoms. The advantageous clinical effects noted in 41 patients who tolerated the drug for a period of 3 months or more are noted in Table I. Borderline cases were always listed in the less favorable category. Among the 97 subjects to whom indomethacin was administered, 41 were benefitted, the drug was discontinued for one reason or another in 50 patients, and 6 were lost to follow-up.

TABLE I.—DEGREE OF BENEFICIAL EFFECTS IN 41 PATIENTS TREATED WITH INDOMETHACIN

Disease	Excellent	Good	Fair
Rheumatoid arthritis (71)	3	14	10
Rheumatoid spondylitis (6)		1	2
Reiter's syndrome (4)		3	
Gout, chronic (5)		1	
Osteoarthritis (4)		2	
Acute gout (1)	1		
Psoriatic arthritis (1)		1	
Causalgia (1)		1	
Erythema nodosum (1)		1	
Scleroderma (2)			
Adiposa dolorosa (1)			
Total (97)	6	23	12

Note: Figures in parentheses total treated in each category.

In 71 patients with rheumatoid arthritis, improvement was excellent in 3, good in 14, and fair in 10. Ten of the 37 subjects with rheumatoid arthritis who stopped taking the drug had noted improvement. This response was not graded, however, because of the short duration of drug administration in most of these patients. Excellent results also were noted in one patient with erythema nodosum, one with acute gout, and one with both osteoarthritis and rheumatoid arthritis. If there were beneficial effects, they were almost always noted within the first 24 to 48 hours, usually after the first or second dose of indomethacin.

The 41 patients who responded favorably have been treated from 3 to 12 months. The dose has ranged from 100 mg. to 400 mg. daily, and for the most part the beneficial effect does not seem to be dose-related. Rarely have we noted greater improvement when the dose was increased in a patient who had not responded to a lower dose.

Indomethacin was evaluated in 17 patients, of whom 12 were started on the drug and 5 on placebo. After one week, the drug and placebo were exchanged without the patient's knowledge. Six of the 17 patients were clinically unaffected by either agent, although 2 stated that they were "benefited" at a time they were taking the placebo. Three of the 5 patients receiving placebo followed by drug benefited from the change. All 8 subjects who received the drug (with benefit) followed by placebo experienced severe exacerbations within 24 hours of the change. One patient had a severe exacerbation lasting 4 days, after which he was symptomatically the same as when taking indomethacin. Once again he was given the drug, but derived no further benefit. The experience in this case casts some doubt upon the validity of accepting an exacerbation which occurs after a drug has been discontinued or replaced by a placebo as proof of the drug's efficacy.

Six patients out of 8 had exacerbations of symptoms on a trial discontinuation of the drug. In most cases the exacerbation that followed substitution of the placebo for the drug exceeded in severity the clinical state prior to indomethacin treatment. In 5 of the 44 cases the indomethacin appeared to become less effective with the passing months. This, of course, may have been the result of altered activity of the disease.

Two patients were unable to take the medication during the day because of lightheadedness, but were able to sleep uninterrupted and had no morning gel when taking indomethacin before sleep only. Both had previously awakened frequently to "loosen up" and had considerable morning stiffness and pain. One patient with psoriasis and arthritis had a remission of the dermatitis coincident with that of the arthritis and an exacerbation of both when placebo was substituted. In most cases existing effusions did not change perceptibly. The erythrocytic sedimentation rate was unaltered despite clinical improvement.

## ADVERSE EFFECTS

There were substantial adverse reactions in the study. Thirty-seven of the 97 patients (37 percent) found it necessary to discontinue the medication after a short period because of adverse effects (Table II). Thirteen patients experienced neither benefit nor side effects, despite a stepwise increase in dose to 400 mg. daily. Six patients did not return.

TABLE II.—SIGNIFICANT ADVERSE EFFECTS FROM INDOMETHACIN IN 97 TREATED PATIENTS

Disease	Number treated	Headache	Peptic ulcer	Other gastrointestinal symptoms	Lightheadedness and dizziness	Mixed symptoms	Other <sup>1</sup>	Total	Percent
Rheumatoid arthritis	71	5	6	6	8	4	3	32	45
Rheumatoid spondylitis	6	1	—	—	—	—	—	1	—
Reiter's syndrome	4	1	—	—	—	—	—	1	—
Osteoarthritis	4	—	—	—	1	—	—	1	—
Scleroderma	2	1	—	—	—	—	—	1	—
Adipositis dolorosa	1	—	—	1	—	—	—	1	—
Total	—	8	6	7	9	4	3	37	—

<sup>1</sup> 1 each: ankle edema, abnormality of glucose tolerance, and urticaria.

The major reasons for discontinuation of indomethacin were, in order of frequency, gastrointestinal symptoms, lightheadedness, giddiness, headache, and psychic changes (Table II). In almost all cases the adverse effects were evident within hours or a few days. Occasionally, gastrointestinal symptoms did not develop for a week.

Nine patients had to stop taking the drug because of lightheadedness, giddiness, loss of equilibrium, inability to concentrate, and dissociation of mind and body. No neurological signs were evident, although a majority of the patients had discontinued the drug before they were examined again. One subject had a syncopal attack and fell, sustaining minor injuries. Four patients who were still taking indomethacin had similar symptoms which, however, were mild and transient.

Seven patients had bothersome gastrointestinal complaints which necessitated discontinuation of the drug, and another 5 had transitory symptoms but were able to continue with the medication as the symptoms lessened. The symptoms included epigastric burning, nausea and vomiting, diarrhea, and melena. Peptic ulcer developed in 6 of the 97 patients (6 per cent). In each case the drug was stopped immediately. Three of these patients were also taking small doses of prednisone (5 to 10 mg. daily), but each had been on a corticosteroid preparation continuously for several months at least, often in the higher dosage range, without epigastric distress. In one patient, a 60-year-old woman with advanced active grade IV rheumatoid disease, who was on prednisone 7.5 mg. per day and indomethacin 250 mg. per day, a prepyloric ulcer perforated into the lesser omental sac 4 months after treatment with indomethacin, with only 4 or 5 days of mild epigastric symptoms.

Four of the 6 patients who developed ulcer did so very rapidly after receiving indomethacin. Epigastric distress usually began after the first two or three doses. In one patient, a prepyloric ulcer was demonstrated 48 hours after the start of treatment and 24 hours after the onset of symptoms. Only 1 of the 6 patients had a prior history of ulcer, which was known to have healed. Antacids were not given routinely since this was not part of our protocol in the early phases of study. Antacids, however, were used in most of the patients late in the study.

Headache developed in 13 patients, 8 severe enough to discontinue the drug. There was no apparent pattern as to location, although the bifrontal type was the most common. Both steady and throbbing headaches were encountered. Although most patients with headaches had an accentuation of symptoms shortly after each dose, 2 reported partial relief of their headaches after each dose of medication and an accentuation of headache proportional to the length of time between medication. Three subjects were given ergotamine tartrate with caffeine without relief of headache.

Urticaria developed in one patient on two separate occasions following ingestion of indomethacin. However, she had had urticaria once previously without known

cause. A patient with rheumatoid arthritis had ankle edema on two separate trials of indomethacin.

#### LABORATORY FINDINGS

Almost all patients had a large number of laboratory examinations before treatment was begun. There was the expected high percentage of moderate anemia and elevated erythrocyte sedimentation rates. Other pretreatment laboratory abnormalities included moderately increased Bromsulphalein retention in 5 patients with rheumatoid arthritis, elevated SGOT levels (3 patients), elevated serum alkaline phosphatase (1 patient), and elevated serum uric acid (4 patients). A not unexpectedly high percentage of patients with reversed albumin/globulin ratio was also found.

Complete blood count, urinalysis, and erythrocytic sedimentation rate were all performed routinely and repeatedly in follow-up. With two exceptions, no pattern of change was noted that could not be attributed to chance or spontaneous variation in disease activity. Other laboratory examinations performed randomly in the follow-up period, which showed no abnormalities, were: serum creatinine (19 determinations), serum uric acid (23 determinations), albumin/globulin ratio (21 determinations), serum bilirubin (17 determinations), cephalin flocculation (18 determinations), and thymol turbidity (22 determinations). Five of 51 patients had guaiac-positive stools. Of these, 2 had melena without radiologically demonstrable cause and 3 had peptic ulcer.

One subject with diabetes mellitus noted increased glycosuria after starting indomethacin. The patient was then studied on a constant dosage of aspirin, with and without indomethacin. While on indomethacin, the glucose tolerance curve appeared to be more abnormal; on 200 mg. of indomethacin daily, there was 0.5 per cent to 2.0 per cent glycosuria, whereas it was negative to 0.5 per cent before medication.

Other abnormalities were noted in 2 patients with rheumatoid arthritis while on treatment, but neither had control determinations for the specific abnormality. One had a serum SGOT of 106 and a serum pyruvic oxaloacetic transaminase (SGPT) of 123 after 2 weeks of treatment. Two weeks after discontinuation of the drug, the SGOT was 37 and SGPT was 46. Indomethacin was then administered for 5 days, after which the SGOT was 53 and the SGPT 56. The patient had no clinical signs that could be related to the changes and had symptomatic relief of the arthritis. The second patient was found to have a serum alkaline phosphatase of 25 King-Armstrong units (normal 2.9) 3 weeks after starting indomethacin. Bilirubin and transaminase were normal. The drug was discontinued and over the next 6 weeks the alkaline phosphatase slowly fell to normal.

#### DISCUSSION

The discovery of a new class of compounds with antirheumatic effects is a significant advance. Indomethacin is not related chemically to the salicylates, pyrazalones, or corticosteroids, and yet in many respects it seems to operate like them. The way in which indomethacin induces symptomatic relief is unclear. The compound possesses antipyretic, analgesic, and perhaps "anti-inflammatory" effects, although specific histologic evidence on the latter point is so far lacking in man. The dramatic effect of indomethacin in cases of acute gout<sup>37</sup> suggests actions resembling those of the corticosteroids. In the rheumatic diseases indomethacin is, in some respects, nonspecific in its action, since symptomatic relief is obtained in a variety of conditions; rheumatoid arthritis, gout, Reiter's disease, ankylosing spondylitis, osteoarthritis of the hip, and other conditions.<sup>1456910</sup>

So far, it has not been possible for us to select the patients who will respond to indomethacin. Our observations seem to indicate that indomethacin does not specifically alter the basic rheumatoid process or that of other diseases which have been treated. Synovial effusions have generally persisted, and the sedimentation rate and titer of rheumatoid factor have not decreased significantly. Where these have improved, in a few cases, the change probably was a result of the natural course of the underlying disease.

The incidence of adverse effects from indomethacin is unfortunately high. Annoying headache and gastrointestinal irritation come soon after the drug has been given. We have found no satisfactory way of overcoming them. The more serious problem of peptic ulcer aligns indomethacin with other established antirheumatic agents. Most of the ulcers in our series were noted in the latter

months of the study; hence, we were not as cautious with the use of prophylactic antacids or other measures as we otherwise might have been. Early in the series we carefully checked stools for blood with no positive results. It should be emphasized that this study was conducted completely with the use of a now obsolete compressed tablet which was subsequently shown to have a variable dissolution rate and erratic absorption.<sup>2,5,10</sup> When a new formulation of indomethacin was used, and a smaller daily dose employed, the incidence of toxic and adverse effects was said to have been reduced.<sup>9</sup>

The discovery of a new type of antirheumatic agent is notable. However, indomethacin is by no means the ideal agent because of the large number of patients who do not respond favorably and because of large number of adverse effects which it induces. It is hoped that related substances may prove to be effective antirheumatic agents and free of serious adverse effects.

#### SUMMARY

Indomethacin, a new nonsteroidal compound, was tested in 97 patients. Results were excellent in 6, good in 23, and fair in 12. The drug was discontinued in 50 patients, and 6 others were lost to followup. The most common reason for discontinuation of the drug was gastrointestinal side effects, which includes 6 cases of peptic ulcer. Although the ratio of adverse to beneficial effects is high, the significant and symptomatic relief which many rheumatoid and other rheumatic patients experience suggests the possibility that a related drug may be found with a more acceptable therapeutic ratio than that of indomethacin.

This study was supported by a grant from Merck Sharp & Dohme, Inc.

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THE COLUMBUS MEDICAL CENTER,  
Columbus, Ohio, June 12, 1963.

NELSON H. REAVEY CANTWELL, M.D., Ph. D.,  
Merck Sharp & Dohme Research Laboratories,  
Division of Merck & Co., Inc.,  
West Point, Penn.

DEAR DR. CANTWELL: Our interest in the therapeutic effects of Indomethacin has been centered largely on Rheumatoid Arthritis, both peripheral and spinal. In reviewing and analyzing our data, I have come to the conclusion that 61 patients have had sufficient trial to be included in our study. Of these, 49 were of the peripheral and 12 of the spinal variety. A good (decisively beneficial) effect was

obtained in 45 (in all of the spinal) and only a fair (indecisive) effect was obtained in 10. No benefit was noted in 6.

The duration of treatment was sufficiently long to permit good clinical observation, being between 12 and 18 months in at least 22 of the patients. As you know, placebos were used, both in single and double blind and 128 relapses were produced by substituting placebo.

As regards dosage, the spondylitics uniformly required less than the peripherals and the daily dose for them varied from as low as 50 mg. to 200 mg. with an average of about 125. In the peripheral arthritis, the average therapeutic dosage level was about 200 to 250 mg. daily. However, in many cases, the dose was taken up to 300 and higher and at least 6 patients received 400 mg. daily for at least one week. Few improvements were noted in the peripheral arthritis group at dosage levels of 150 mg. daily. Most of the peripheral arthritics are now being carried on a daily dose of 300 mg. daily but a significant number are benefitted to a striking degree on 200 mg. daily.

The greatest deterrent to increasing dosage to an effective level is the appearance of cerebral toxicity. This manifests itself clinically in excruciating severe headaches, dizziness, lightheadedness, disturbances of sensorium, a feeling that the head is floating away or even separating from the body and feelings of detachment from reality.

The higher the dose, the more severe the symptoms but there was some variation in individual susceptibility. A few individuals experienced considerable toxicity at levels of 100 mg. daily whereas, a goodly number could take 300 mg. a day without any adverse symptoms. However, the usual appearance of symptoms was at the range of about 200 to 225 mg. although cerebral toxicity occurred in over half of our patients, that is 31 out of 61. In 80% of these, the toxicity could be adequately ameliorated or abolished by reduction in dosage. We did not run a specific questionnaire regarding an antecedent history of migraine but a prominent history of headache was present in only about 8 to 10.

I trust the above will provide you with the information you desire. If however you desire additional information, please let me know.

Yours truly,

NORMAN O. ROTHERMICHL, M.D.

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COLUMBUS MEDICAL CENTER RESEARCH FOUNDATION, INC.

*Columbus, Ohio, July 3, 1963.*

NELSON H. REAVEY CANTWELL, M.D., Ph. D.  
Merck Sharp & Dohme Research Laboratories.  
Division of Merck & Co., Inc.,  
West Point, Pa.

DEAR NELSON: Enclosed is the Indomethacin questionnaire which you asked me to fill out from our work. As you know, we have interested ourselves almost exclusively in the beneficial effect of Indomethacin on rheumatoid arthritis and have used it only sporadically and in a random way on other rheumatic disorders. We have chosen to exclude the latter groups since they have not been formally organized and analyzed.

From the nature of the questionnaire, you must understand that all of our patients have been treated for a greater or less period of time with 150 mg. or less and hence are included on the questionnaire but in a significant number of these, the dose was raised to a much higher level to achieve a satisfactory result. Consequently, the number listed under unimproved should not be looked upon as the total number of Indomethacin failures. Furthermore, the number experiencing headache is given as that number which occurred at the dosage range of 150 mg. or less. As you know, we had a considerably higher incidence of cerebral toxicity at higher dosage levels. These data are well explained in my previous report to you several weeks ago. The one case of bleeding was probably from a diverticulum and not ulcer and furthermore is not included among those who experienced gastrointestinal symptoms since his only symptom was that of weakness and faintness.

We are in the process of trying to develop satisfactory control techniques for determinations of Indomethacin blood levels. I don't see how you can possibly refute the finding of a zero blood level in every instance where blood was drawn 24 hours after the preceding dose. We hope to resolve this question.

As you know, we are also keenly interested in whatever effects, if any, Indomethacin may have on tryptophane and serotonin metabolism and how this may relate to the disease of rheumatoid arthritis.

Best wishes always.

Sincerely yours,

NORMAN O. ROTHERMICHL, M.D.

INDOMETHACIN QUESTIONNAIRE, JUNE 19, 1963

Name of Investigator: Norman O. Rothermich, M.D.

- |  |    |
|--|----|
| 1. How many patients have been treated with 150 mg. or less?   | 60 |
| a. Number who experienced relief of pain?-----   | 40 |
| b. Number who experienced relief of swelling & inflammation?-----  | 40 |
| c. Number who had definite over-all improvement?-----  | 40 |
| d. Number unimproved?-----   | 20 |
| 2. How many of the above patients experienced headache?-----   | 15 |
| 3. Of those who had headaches  |    |
| a. how many had to discontinue the drug because of it?-----  | 8  |
| b. how many became tolerant of the headache and continued on the drug?-----  | 3  |
| c. how many had relief of their headache at a lower dosage?-----   | 4  |
| 4. How many of the patients experienced gastrointestinal symptoms (abdominal distress, nausea, vomiting, etc.)?----- | 3  |
| a. How many had to discontinue the drug because of these symptoms?-----  | 0  |
| b. How many developed a definite ulcer or bleeding?-----   | 1  |
| 5. How many of your treated patients have  |    |
| a. chronic rheumatoid arthritis?-----  | 48 |
| spondylitis?-----  |    |
| b. Arthritis or inflammatory disorders other than chronic rheumatoid arthritis? -----                                | 12 |
| 6. Does acute inflammatory disease respond better than chronic disease?-----   | No |

NORMAN O. ROTHERMICHL, M.D.

COLUMBUS MEDICAL CENTER RESEARCH FOUNDATION, INC.,

*Columbus, Ohio, October 9, 1962.*

NELSON H. REAVEY CANTWELL, M.D., Ph. D.,  
Merck Sharp & Dohme Research Laboratories,  
Division of Merck & Co., Inc., West Point, Pa.

DEAR NELSON: A special report to you is in order regarding the appearance of an adverse effect of the new drug, MK-615, now under investigation. This effect is an entirely symptomatic one and as yet not measurable by any objective methods. The patient complains of a distressing lightheadedness, a feeling of "the head being in outer space", a feeling of the head being foggy and a feeling of difficulty in concentration or in cerebration. There may or may not be an associated violent headache and in a few cases, the headache was so violent that it was predominant or alone. In a few instances, these symptoms have been so severe as to be totally incapacitating and even prostrating.

The physical findings at this time are not remarkable. The ocular fundi are negative and there is no papilledema. The neurologic examination is likewise negative in all other respects. In a few instances, the electroencephalogram has shown no decisive or characteristic changes. Other laboratory studies are not changed significantly during these episodes. The spinal fluid has not been studied.

In general, this adverse effect appears to be a dosage related phenomenon and in most cases, does not appear until 250 mg. daily has been reached. However, there is a considerable variation in individual susceptibility to this effect. Some patients have been on 300 mg. or more daily for some time without any adverse effects. Some patients have felt this effect at dosages as low as 150 mg. daily. It is definitely reproducible in the same patient at approximately the same dosage levels. There appear to be no residuals from this adverse effect. Symptoms disappear usually within 24 to 48 hours after discontinuing the drug. The antirheumatic effects of the drug are not reduced by this effect. As a matter of fact, the antirheumatic effect may be very striking at these higher dosage levels. In some severe arthritics, it has been impossible to control the arthritis without producing these adverse effects. As of this date, 16 patients have had toxic effects out of a total of 49 patients receiving the drug. No other ill-effects of the drug have been noted.

Yours truly,

NORMAN O. ROTHERMICHL, M.D.

THE COLUMBUS MEDICAL CENTER,  
Columbus, Ohio, October 12, 1963.

NELSON H. REAVEY CANTWELL, M.D., Ph. D.,  
*Merck Sharp & Dohme Research Laboratories,*  
*Division of Merck & Co., Inc., West Point, Pa.*

DEAR DR. CANTWELL: The results of our experiences with the capsular form of 'Indocin' are contained in detail on the enclosed summary tables.

There can be no doubt that 'Indocin' does have clinically observable antirheumatic effect. This effect is uniformly consistent at comparatively low dosage levels in the rheumatoid spondylitic. It is in this particular disease that phenylbutazone and derivatives have been particularly effective but it would appear that 'Indocin' is equally effective at a slightly lower dosage level and, of course, without any of the life-threatening adverse effects which so often complicate therapy with the former compounds. In other words, it is my belief that in rheumatoid spondylitis, 'Indocin' can do as much for the patient as phenylbutazone but do it with comparative safety.

In the peripheral rheumatoid arthritis, there is considerable variation from one patient to the next and sometimes in the same patient from one time to another in the ability of 'Indocin' to exert a consistently and significantly beneficial effect. There is no doubt that higher dosage levels are required than in the case of the rheumatoid spondylitic. As higher dosage levels are approached, it is to be expected that the incidence of cerebral toxicity goes up proportionately and this, in my opinion, represents a not insignificant disadvantage to the drug for it reduces the number of arthritics who can be benefited by the drug and also reduces the degree of benefit in a given arthritic because it necessarily puts a ceiling on maximum maintenance dosage. This is particularly frustrating because I am personally convinced that this cerebral toxicity does not threaten the life of the patient nor does it leave any permanent residuals. In fact, there is usually prompt subsidence of the cerebral toxic symptoms within comparatively few hours (usually 12 to 24) after the drug has been discontinued. Most of the time, the drug can be resumed at a lower dosage level without a recurrence of the cerebral toxicity. It is quite apparent from the chart that we have been able to carry some patients on a comparatively high maintenance dose and, of course, this implies that these patients did not have enough cerebral toxicity for them to wish to be taken off the drug or have it reduced in dosage.

On the other hand, some patients have developed disabling cerebral toxicity usually in the form of severe vertigo, lightheadedness or violent headaches on comparatively low doses. One patient tried on three separate occasions to take a 25 mg. capsule but just on the one dose developed such a violent headache that he could not continue it. On the other hand, another patient had been on 50 mg. and h.s. for at least a year when his vertigo and lightheadedness had increased to a disabling degree and required him to discontinue the drug temporarily. One other patient developed a violent toxic reaction after only one week of therapy and had to be confined to bed, more or less continuously, for four or five days. One patient while on a ladder working became dizzy and fell off suffering a fractured arm. Another busy executive became so dizzy and lightheaded that he feared crossing the street against all traffic.

It would seem worthwhile to list the various manifestations which I have chosen to lump together under the designation of cerebral toxicity:

1. Headache.
2. Vertigo (usually not true room-spinning).
3. Lightheadedness.
4. Feelings of fogginess in the head.
5. Sometimes difficulty in concentration.
6. Occasional feelings of unreality.
7. Marked stimulation with resultant insomnia. Very similar in designation to caffeine effect.
8. In higher doses, some ataxia and even personality change, more toward a paranoid state, were observed.

It is my belief that the capsule is superior to the tablet only in that it permits for a more consistently reliable rapidity of absorption whereas the tablet form varied greatly in its rate and degree of absorption. However, it cannot be said that the capsule has reduced the incidence of cerebral toxicity.

At the same time, "Indocin" is notably free of other toxic effects. A few patients complain of some stomach pain but these were rarely consistent and reproducible. There were no deleterious effects on the formed elements in the peripheral blood including the red and white corpuscles and platelets. There were no alterations of

any of the chemical elements of the blood. Notably, we could not find any consistent elevation of the BUN. All liver function studies remained normal during therapy and there were no evidences of any ill-effects on the kidneys or lower urinary drainage structures. No cardiovascular effects could be detected. The drug did not have any reproducible effect on the Latex Fixation Test nor was there any significant effect on the Sedimentation Rate regardless of the clinical response. No effects on the skin were observed and there were no changes in the lower bowel or the bowel habits. The drug had no apparent effects on appetite or on muscle strength.

In summary, "Indochin" would appear to be an excellent therapeutic vehicle for treating rheumatoid spondylitis. In the very few cases where it was tried, it seemed to have a beneficial effect on acute attacks of gout. It did not seem to influence materially cases of generalized chronic fibrositis or acute localized periarticular fibrositis nor did it have any beneficial effect on back problems, especially posterior cervical fibrositis. In one case of chronic gouty arthritis, it has proved to be dramatically but consistently beneficial to a very high degree over a period of nearly two years. "Indochin" has an "excellent" beneficial effect in some cases of peripheral rheumatoid arthritis but only a "good" effect in a larger percentage and there is complete failure or ineffectiveness in a distressingly high percentage of such cases. In most of these latter cases, it was our feeling that the failure was due largely to the inability to break through the therapeutic ceiling maintained by the cerebral toxicity.

I hope the enclosed summarized data will be helpful to you.†

Cordially yours,

NORMAN O. ROTHERMICH, M.D.

[From Journal of the American Medical Association, vol. 195, No. 13, Mar. 28, 1966, pp. 124-128]

#### AN EXTENDED STUDY OF INDOMETHACIN\*

##### II. CLINICAL THERAPY

(By Norman O. Rothermich, M.D.)

A new antirheumatic drug, indomethacin, was evaluated over a long period of observation (42 months maximum). Clinically satisfactory results listed as both good and excellent were obtained in a high percentage of patients with ankylosing spondylitis, gouty polyarthritis, psoriatic arthritis, and other miscellaneous benign (nonfatal) rheumatic diseases. In rheumatoid arthritis, indomethacin produced good and excellent results in a lesser, though appreciable, percentage of cases and may be regarded as another valuable drug to be added to the overall program of therapy in this notably difficult disease. As indicated in the previous report, the experimental nature of this study required that in some cases the dosages be increased to and beyond tolerance. Therefore, therapy in private practice may not yield as high a percentage of favorable results as indicated in this report.

The present treatment of rheumatoid arthritis still leaves much to be desired. Virtually all therapeutic agents which are believed to have beneficial effect in this disease have limitations on their utility and efficacy because of harmful side effects, usually dose-related. The development of an antirheumatic agent with little or no clinical hazards would be very desirable. In a previous publication,<sup>1</sup> it was reported that indomethacin was not hazardous, except for the possibility of gastric-ulcer formation.

Previous reports have indicated that indomethacin produces significant benefit in certain rheumatic diseases.<sup>2 3 4 5</sup> These reports were based largely on com-

†Retained in committee files.

\*From the Department of Medicine, Ohio State University Hospital, and the Columbus Medical Center Research Foundation, Columbus, Ohio. Reprint requests to 1211 Dublin Rd., Columbus, Ohio 43212.

<sup>1</sup> Rothermich, N.O.: A Report of 42 Months Experience With Indomethacin: I. Clinical Pharmacology. *J.A.M.A.*, to be published.

<sup>2</sup> Norcross, B. M.: Treatment of Connective Tissue Disease With a New Nonsteroidal Compound (Indomethacin). *Arthritis Rheum* 6:290 (June) 1963.

<sup>3</sup> Smyth, C. J.; Valayos, E. E.; and Amoroso, C.: Indomethacin in Acute Gout Using a New Method of Evaluating Joint Inflammation. *Arthritis Rheum* 6:299 (June) 1963.

<sup>4</sup> Rothermich, N. O.: Indomethacin: A New Pharmacologic Approach to the Management of Rheumatic Disease. *Arthritis Rheum* 6:295 (June) 1963.

<sup>5</sup> Hart, F. D., and Boardman, P. L.: Indomethacin: A New Nonsteroid Anti-Inflammatory Agent. *Brit Med J* 2:965-970 (Oct 19) 1963.

paratively short-term observations. The present report will describe clinical experiences with indomethacin which began in November 1961. Our attention was given mainly to its effects on patients with rheumatoid arthritis, but other rheumatic diseases were also treated. Because this was the first trial of indomethacin in the human, small amounts were given initially and effective dosages were not reached until late January 1962. For this reason, the present report deals with experiences during a 42-month period from Feb. 1, 1962, to Aug. 1, 1965.

#### Materials and Methods

The treatment sample comprised 216 patients and 234 patient-trials. This does not include 23 patients on whom therapy was begun but for one reason or another became "dropouts." These will be discussed later. It is noteworthy that 26 patients have been on continuous therapy for 30 months or more, the longest being 42 months. In the treatment sample, there were 147 females and 69 males, and all were adults with the exception of three children ages 9, 11, and 13 years. There were 117 patients with probable, definite, and classical rheumatoid arthritis as defined by the Committee on Diagnostic Criteria of the American Rheumatism Association (ARA); all cases of "possible" rheumatoid arthritis were listed under nonspecific polyarthritis. There were 22 cases of ankylosing spondylitis and 14 cases of chronic gouty polyarthritis (ie, the chronic polyarthritis having characteristics similar to rheumatoid arthritis, but associated with a negative latex titer and a high serum uric acid level and occurring in an individual who has been diagnosed as having gout). In addition, there were 15 cases of osteoarthritis, 29 cases of fibrositis, and 19 cases of other miscellaneous rheumatic diseases as follows: 10 "possible" rheumatoid, 3 juvenile rheumatoid, 2 psoriatic arthritis, and 1 each of Reiter's disease, pseudogout, villonodular synovitis, and Tietze syndrome.

In the initial trials, patients were selected with moderately severe rheumatoid arthritis which was fairly well controlled with the standard basic program of therapy consisting of increased rest, physical therapy, salicylates, and sedation, as well as small doses of corticosteroids and sometimes gold or phenylbutazone therapy or both. The first step was to discontinue administration of all therapeutic agents except salicylates and corticosteroids, or as many as possible consistent with the patient's continued good management and control of the disease process. Indomethacin therapy was initiated in small doses and gradually increased according to the patient's ability to tolerate higher levels. At the same time, a gradual reduction of corticosteroid therapy was begun. If and when corticosteroid therapy could be discontinued entirely, gradual reduction of salicylate therapy was attempted. In some cases all therapeutic agents were withdrawn and control of the disease was continued at the same level on indomethacin alone. (Withdrawal of salicylates was for experimental purposes and is not to be construed as recommended clinical procedure.)

The evaluation of clinical results was based on those factors described in a previous report.<sup>6</sup> Greatest emphasis was placed on the patient's own gradation of his disease from 0 (no symptoms or disability) to 4+ (severe pain, morning stiffness, and total disability) based on his past experience with his disease. In addition, a separate evaluation of disease activity and disability was made by the physician. It is believed that accuracy and objectivity of such gradations can be greatly enhanced and made more secure by liberal use of placebo substitution and by quantitation of the steroid and aspirin requirements of the individual. When used by a clinician interested in the management of rheumatoid arthritis, these criteria can often be as accurate and precise as the many criteria which have more formalized physical and arithmetical indices.

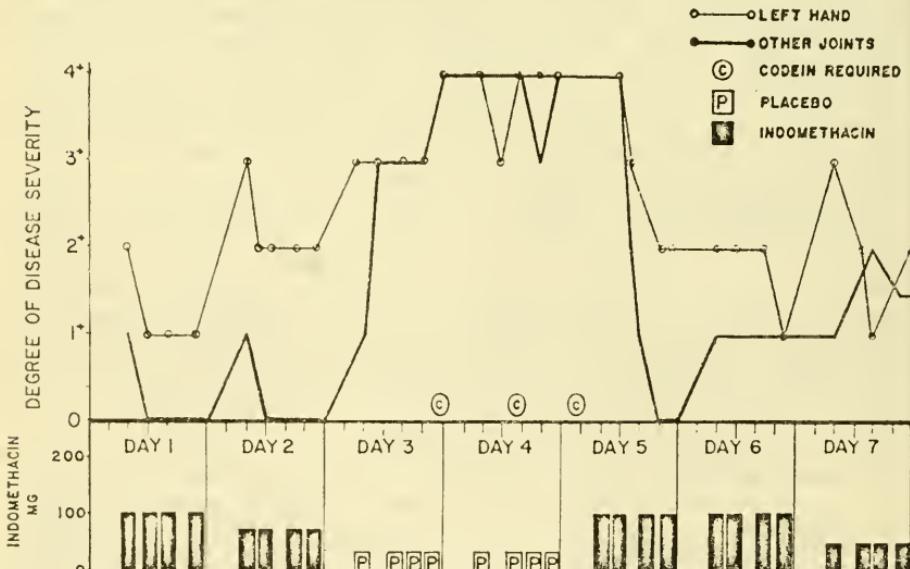
The well-recognized decisively beneficial effects of corticosteroids (and to a much lesser degree of aspirin) provide an excellent base for reference in therapy of rheumatic diseases. Any new agent therefore must be able to reduce materially or eliminate the need for corticosteroids in an appreciable number of cases. After such elimination, therapy may be further evaluated by the ability to reduce the dose of or discontinue salicylate therapy. These have been important criteria in our evaluation of a favorable response to indomethacin. In all cases listed as having had an excellent response to indomethacin, either of these two or the clear-cut, unequivocal placebo relapses have been a required criterion.

<sup>6</sup> Rothermich, N. O.: Clinical Experiences With Indomethacin In Rheumatic Diseases, *Proceedings of the Eighth Congress of the Japan Rheumatism Association, Okayama, Japan, 1964*, pp. 159-163.

In "fresh" cases of rheumatoid arthritis where corticosteroid therapy had not been previously used, a patient was rated as having good or excellent response to indomethacin if evidences of active synovitis, the jelling phenomenon, and painful disability, as indicated by the patient's symptoms and the physician's observations, receded under active drug therapy and promptly exacerbated when placebo was substituted. In some patients, the placebo trials were made several or more times in order to establish with certainty the relapsing character of the disease under placebo influence. In cases other than rheumatoid arthritis, such as spondylitis, psoriatic arthritis, and chronic gouty polyarthritis, therapeutic evaluation was based on control of disease activity on indomethacin alone, with relapses precipitated by placebo substitution. Occasionally, patients would suspect placebo substitution by a change in side effects. For this reason from the statistician's viewpoint, the placebo trials in this report (and probably in most clinical drug reports) cannot be considered as true "blind" studies. Usually there was enough delay in this awareness to permit the therapeutic assessment. Furthermore, the appearance of side effects is often capricious and inconsistent, thus further limiting the patient's ability to detect placebo. In some of these cases, adequate control had previously been achieved by the use of phenylbutazone, and effectiveness of indomethacin could be measured by its ability to replace such therapy.

Placebo substitutions were made in 86 of the patients. In 70 of these, there was decisive clinical relapse on placebo; this was verified on repeated trials in 55 patients. In most instances, placebo was introduced whenever a patient seemed to be established and well-controlled on indomethacin therapy. In addition, at times when an adverse reaction appeared, a placebo was substituted to determine if the adverse reaction was actually due to indomethacin or some other cause. Occasionally, in a patient whose therapeutic response to indomethacin could not be determined with any reasonable accuracy or whose disease continued to progress even though he was on other antirheumatic medications as well, a placebo was administered to observe if actual worsening of disease occurred while administration of other medications was continued in exactly the same dosage. In 21 instances, neither the patient nor the physician was informed of the placebo substitution, and in one such case a striking effect was observed and charted (Fig 1).

FIGURE 1



1. Placebo trial on a 40-year-old woman with severe psoriatic arthritis. Note profound relapse on receiving placebo and partial loss of disease control on day 7 with reduction in dosage.

*Results*

The therapeutic results in rheumatoid arthritis are shown in Table 1. The good and excellent results combined totaled 88 out of 117 (75%). The patients are categorized according to the diagnostic criteria of the ARA into classical, definite, and probable. It is noteworthy that in the classical group, which is notoriously resistant to treatment, the percentage of favorable results was surprisingly high (65%). As might be expected, this was appreciably lower than the 82% in the combined groups categorized as "definite" and "probable." The dosage range was approximately the same in the three different groups; in all patients where no side effects were encountered, the vast majority received a maintenance dose between 100 and 200 mg. In the 88 patients who obtained a good or excellent result, 69 had been receiving a maintenance dosage of corticosteroids at the time indomethacin therapy was begun, and 44 of these were able to reduce the corticosteroid dosage by 25% or more categorized as follows: 3 patients, a dose reduction of 25%; 8 patients, 33½%; 10 patients, 50%; 4 patients, 75%; and 19 patients, 100% (discontinued).

TABLE 1.—RESULTS IN 117 PATIENTS WITH RHEUMATOID ARTHRITIS

Diagnosis	Number of patients	Results		
		Excellent	Good	Poor <sup>1</sup>
Classical.....	55	18	19	18
Definite.....	35	14	14	7
Probable.....	27	16	7	4
Total.....	117	48	40	29

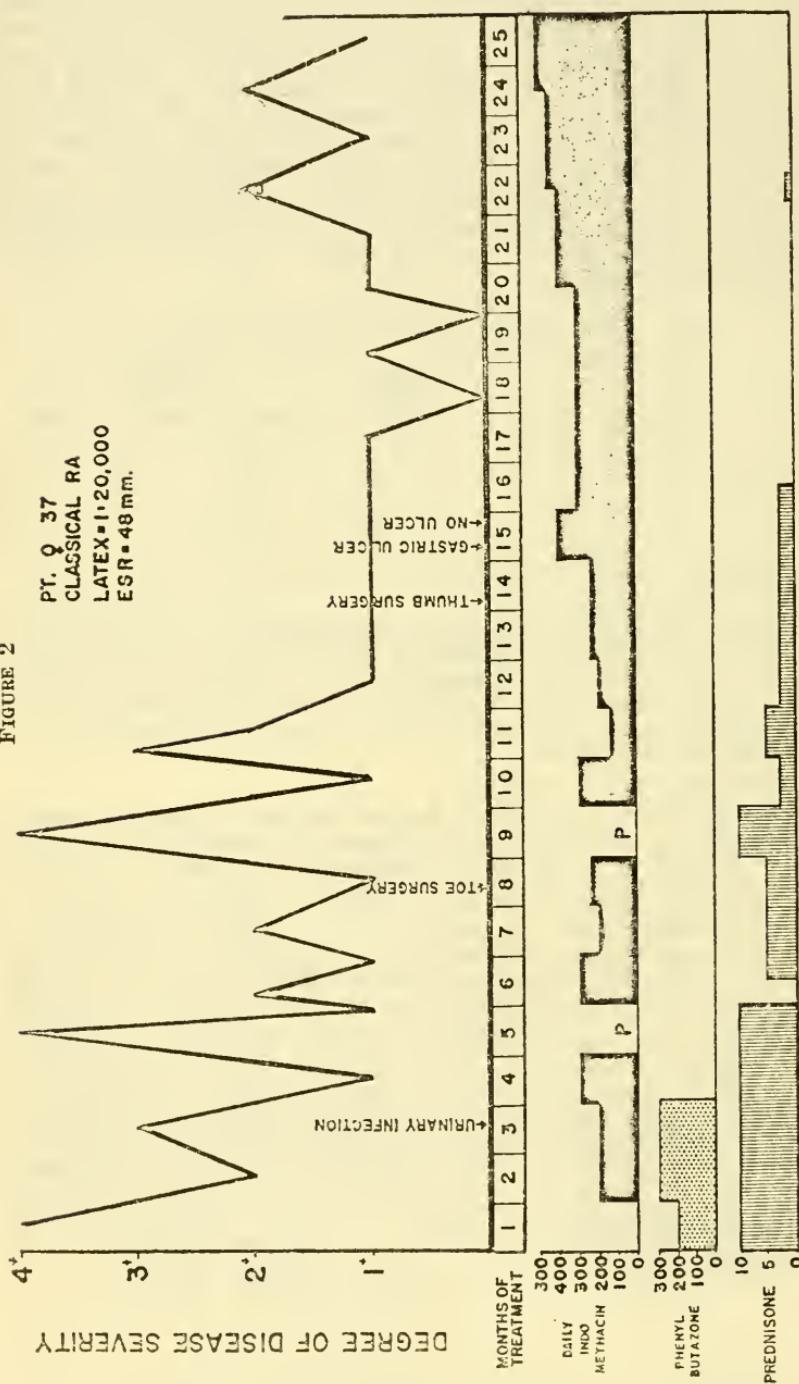
<sup>1</sup> Equivocal or no benefit.

In ten patients with rheumatoid arthritis, administration of the drug had been discontinued for one reason or another for an appreciable period of time. A second and clinically distinct trial of indomethacin therapy was made in these patients. The results were the same in both trials in six of the patients, but in two, the first trial obtained a good result and the second a poor result, whereas in two others the exact opposite held true.

*Illustrative case reports*

CASE 1.—A 37-year-old white woman has had classical rheumatoid arthritis for eight years in an extremely active, progressively disabling form. Several years ago, on large doses of aspirin, she developed a huge gastric ulcer. On a trial of gold therapy, there was mild improvement but toxicity developed. On corticosteroid therapy, there was definite improvement, but this therapy was withdrawn for obscure reasons and she had a severe relapse. Chloroquine phosphate produced severe toxicity and phenylbutazone aggravated the ulcer. When first brought into this study in December 1962, the patient was a stage IV, class IV, with total disability, and the arthritis was in a very active, destructive phase. Treated with small doses of corticosteroid, enteric-coated aspirin, and cautious doses of phenylbutazone, the arthritis was somewhat controlled. Indomethacin therapy was begun and with gradually increasing doses, the arthritis became fairly stable and of questionable activity despite reduction and eventual elimination of all other medications, including salicylates (Fig. 2). After 14 months of indomethacin therapy, the ulcer was reactivated but it healed on treatment while the drug therapy was continued. The patient is now up and about, takes care of her entire household, and occasionally even goes to dances. The total duration of indomethacin therapy was 25 months and the patient had received no other medication for the last ten months.

FIGURE 2



2. Disease activity in patient with classical rheumatoid arthritis. Note elimination of all therapy except indomethacin with continued reasonably good control of disease, and the gastric ulcer appearing and healing on continued high-dosage indomethacin therapy.

In the benign rheumatic diseases other than rheumatoid arthritis, the results are even more encouraging as indicated in Table 2, and the average effective maintenance dose was lower, being only 100 mg. or less in 72% of the cases. Out of 22 cases of spondylitis, there were only three treatment failures, and three such failures were also seen in 14 cases of chronic gouty polyarthritis. In the cases of osteoarthritis, the results were not quite so spectacular, with a good or excellent result in ten out of 15 cases. In the cases of fibrositis, the results were even less favorable, but still impressive with a good or excellent result in 55%. There was a high percentage of benefit in the miscellaneous group of disorders which comprised for the most part those cases with chronic polyarthritis of an indeterminate nature which would otherwise have qualified as "possible rheumatoid arthritis," according to the ARA classification. Also in this miscellaneous group and deserving of special mention are two cases of severe psoriatic arthritis (ie, cases having the clinical characteristics of rheumatoid arthritis and active psoriasis but with a negative latex titer) in which there was a dramatically beneficial effect on the arthritis, but no effect whatever on the psoriasis.

TABLE 2.—RESULTS IN 99 PATIENTS WITH MISCELLANEOUS RHEUMATIC CONDITIONS

Diagnosis	Number of patients	Results		
		Excellent	Good	Poor <sup>1</sup>
Rheumatoid spondylitis.....	22	15	4	3
Gouty arthritis.....	14	10	1	3
Fibrositis.....	29	12	4	13
Osteoarthritis.....	15	4	6	5
Miscellaneous.....	19	10	4	5
Total.....	99	51	19	29

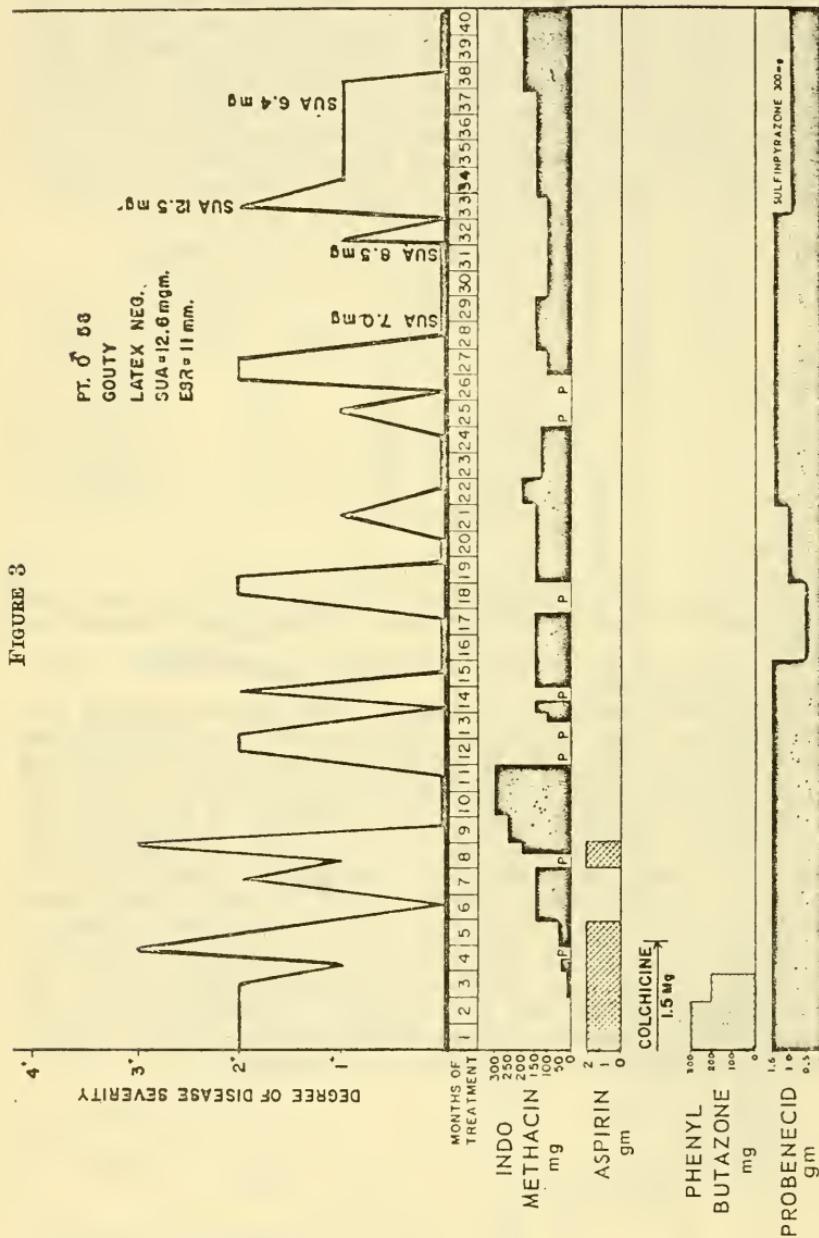
<sup>1</sup> Equivocal or no benefit.

In eight patients, a repeat clinically distinctive trial of therapy was made and the result was the same in five cases, while in three, the results changed from poor to good.

The following case is an illustration of indomethacin effectiveness in a patient with nonrheumatoid arthritis.

CASE 2.—A 56-year-old white man developed a very severe, disabling polyarthritis five years previously. He was in continuous pain, unable to work and having extreme early-morning stiffness. He had been known to have gout, and serum uric acid determinations were quite high (10–12 mg/100 cc). As a result of treatment with salicylates, corticosteroids, colchicine, and phenylbutazone, there was considerable improvement in his arthritis but he was still left with occasional joint pain and tenderness and some early-morning stiffness. Indomethacin therapy was begun in January 1962 and gradually administration of all other antirheumatic drugs was discontinued (Fig. 3). In later months, relapse occurred apparently associated with failure of the uricosuric drug. A change in the uricosuric drug again brought the serum uric acid level to normal and remission was again achieved with administration of indomethacin alone. The patient is well with no indications of rheumatic disease, although relapses occur whenever he is given placebo. The total duration of indomethacin therapy was 42 months, and the patient has received no other medication except probenecid and then sulfinpyrazone (Anturane) for the past 38 months.

FIGURE 3



3. Disease activity in patient with chronic gouty polyarthritis. Before indomethacin therapy, phenylbutazone, colchicine, and aspirin were given with only fair disease control. Note the prompt relapses with each placebo trial. SUA = serum uric acid.

*Comment*

Indomethacin is effective in the control of certain cases of rheumatic diseases. The high percentage of good and excellent results in nonrheumatoid benign rheumatic diseases would suggest that it is the treatment of choice. The initial dose may be 25 mg once or twice daily. In this group of diseases, it is seldom necessary for the physician to exceed a total daily dose of 100 mg or 125 mg at the most. However, even with low dosage the physician must be on guard for the occasional patient who might develop gastric upset or even ulceration, as well as the unusual patient who is highly susceptible to cerebral side-effects.

In rheumatoid arthritis, indomethacin is also effective, producing a good and excellent result in an appreciable number of cases, and because of its limited hazards, it should be included among the therapeutic weapons to be used in the treatment of this difficult disease. However, it should not be inferred that indomethacin replaces or eliminates the need for a sound basic therapeutic program for the patient with rheumatoid arthritis which should include increased rest, salicylates, physical therapy, and other adjunctive or supportive measures. The patient with rheumatoid arthritis who is not responsive to the basic program of therapy may have this supplemented by the cautious prescribing of indomethacin beginning with a dose of 25 mg two or three times daily, best given after meals and at bedtime with a glass of milk. The daily dose may be increased in increments of 25 mg at perhaps weekly intervals. If disease activity persists, the physician would be justified in increasing the total daily dose to 150 to 250 mg daily, according to tolerance. As the higher dosage of indomethacin is approached, the physician must increase his caution regarding the possible development of gastric ulcer and in some patients must be prepared to cope with the distressing symptoms of headache, lightheadedness, and disturbances of sensorium. If the rheumatoid arthritic process continues to remain actively painful and disabling, the physician may cautiously add to the overall program such therapy as gold and low-dosage corticosteroid therapy as recommended in previous reports.<sup>7,8</sup>

*"Dropouts"*

In accordance with the suggestion of Mainland and Sutcliffe,<sup>9</sup> an explanatory note is appended regarding patients who were dropped from the study.

Twenty-three patients who began therapy, for one reason or another, became dropouts. They are grouped in four main categories: (1) Five patients were simply lost to followup for inexplicable reasons. Some were doing well and some were not doing so well. (2) There were four patients in whom the original diagnosis was determined to be incorrect. (3) Six patients were finally determined to be impossible to evaluate, despite the liberal use of placebo. Some of these at one time were considered to yield excellent results and at another time, seemed to be therapeutic failures. However, while honest and objective appraisal was attempted, retrospectively it was decided that there was too much uncertainty regarding their evaluation to permit conclusions in one direction or another. (4) Eight patients were receiving the drug for so brief a time that no conclusions could possibly be warranted. Most of these were too disturbed at the prospect of experimentation, after they had to sign "release form." Two others unexpectedly had to move out of town within a week after therapy was started.

*Generic and Trade Names of Drugs*

Indomethacin—*Indocin*.

Phenylbutazone—*Butazolidin*.

Chloroquine phosphate—*Aralen Phosphate*.

Prednisone—*Deltasone, Deltra, Meticorten, Paracort*.

Probeneid—*Benemid*.

Sulfinpyrazone—*Anturane*.

<sup>7</sup> Rothermich, N. O.: Local Steroid Injection Therapy in Rheumatic Diseases, *Postgrad Med* 30:283-292 (Oct) 1961.

<sup>8</sup> Rothermich, N. O.: Corticosteroid Therapy in Rheumatoid Arthritis, *Postgrad Med* 36:117-128 (Aug) 1964.

<sup>9</sup> Mainland, D., and Sutcliffe, M. I.: The General Problem of Dropouts, ARA Coop Clin Committee Bull 18:6 (Dec 7) 1964.

Senator NELSON. We will recess until tomorrow morning at 10 a.m.

(Upon the direction of the chairman, the letter by Mr. T. O. Cron, Assistant Commissioner for Education and Information, FDA, subsequently dated, follows:) <sup>1</sup>

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,  
FOOD AND DRUG ADMINISTRATION,  
*Washington, D.C., May 3, 1968.*

Hon. GAYLORD NELSON,  
*Chairman, Subcommittee on Monopoly, Select Committee on Small Business,  
U.S. Senate, Washington, D.C.*

DEAR SENATOR NELSON: You will recall that Dr. Robert McCleery of our Bureau of Medicine testified before your Subcommittee yesterday and noted that an article in *Pageant* magazine misrepresented the safety and effectiveness of Indocin (indomethacin). While Dr. McCleery was testifying, Merck & Co., manufacturers of the drug, distributed a statement of rebuttal.

Three major points were made in the company's release: (1) that the FDA had never discussed this matter with the company; (2) that the company neither encouraged publication of the article nor supplied testimonial letters on unapproved claims; and (3) that the company did not see the text before it appeared in print.

For the record, the *Pageant* article was indeed discussed with the Merck management, including its President, on November 11, 1966. I was present at that meeting. Prior to that, our Agency received letters from the company's Vice-President for Public Relations and its Administrative Vice-President about the article and its creation.

In addition, both Vice-Presidents had acknowledged to us in writing that Merck had supplied "case histories" (another term for testimonials) to the authors of the magazine article. Finally, the letter from Merck's Vice-President for Public Relations enclosed an internal memorandum written to the Administrative Vice-President, dated June 17, 1966, which demonstrated that the company's public relations staff had seen the *Pageant* article and had not registered disapproval. This was, of course, before the July publication date of the magazine.

I hope this letter is helpful to the work of the Subcommittee.

Sincerely yours,

THEODORE O. CRON,  
*Assistant Commissioner for Education and Information.*

(Whereupon, at 2:35 p.m., the subcommittee recessed, to reconvene at 10 a.m., Friday, May 3, 1968.)

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<sup>1</sup> See p. 3370, *infra*.

# COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

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FRIDAY, MAY 3, 1968

U.S. SENATE,  
MONOPOLY SUBCOMMITTEE OF THE  
SELECT COMMITTEE ON SMALL BUSINESS,  
*Washington, D.C.*

The subcommittee met, pursuant to recess, at 10:10 a.m., in room 318, Old Senate Office Building, Senator Gaylord P. Nelson (chairman of the subcommittee) presiding.

Present: Senators Nelson, Scott, and Hatfield.

Also present: Benjamin Gordon, staff economist; James H. Grossman, minority counsel; Susan H. Hewman, research assistant; Elaine C. Dye, research assistant; and William B. Cherkasky, legislative director, staff of Senator Nelson.

Senator NELSON. The hearings of the Subcommittee on Monopoly will open. We will hear testimony this morning from representatives of Merck & Co., who will be introduced by the distinguished and very able Senator from New Jersey, Mr. Case.

Senator, I understand you will introduce the representatives of this very fine company, which is located in your State.

## STATEMENT OF HON. CLIFFORD P. CASE, A U.S. SENATOR FROM THE STATE OF NEW JERSEY

Senator CASE. Thank you, Mr. Chairman. It is indeed located in New Jersey, and I guess a lot of other places, too, but we claim it as a citizen. Also, as a citizen of Rahway, N.J., we claim it as a citizen of my hometown. That makes it a special pleasure and privilege to present to you this distinguished citizen of my town, represented by its chief executive and several of its leading scientists.

Two of the witnesses are constituents, New Jersey residents and personal friends of mine: Mr. Henry Gadsden, president of Merck & Co. on my right, and Dr. Max Tishler, who is president of Merck, Sharp & Dohme research laboratories division. As a matter of fact, Dr. Tishler and I were remembering that 31 years ago, when I first ran for public office in the Common Council of the great city of Rahway—

Senator NELSON. That is at the head of the Boy Scouts. I remember that.

Senator CASE. Senator, you are so disarming.

He opened his door to me when I was ringing doorbells in the approved fashion and seeking votes. So if he is a good friend, I think we have good reason to be.

Senator NELSON. Did you check the vote in that precinct?

Senator CASE. This vote was 10 to 1. This was a good, solid, American precinct.

I am glad to say it is more or less in the State, sir.

The other two witnesses, Mr. Chairman, are Dr. Karl Beyer, senior vice president for research, and Dr. Douglas Lawrason.

They are from the State of the senior Senator from Pennsylvania, also on the Senate Small Business Committee, who is here this morning.

Senator SCOTT. I will give you as much time as you want to say something nice about me, although you may defer.

Senator CASE. If it is all right, Mr. Chairman, I shall defer this until the Senator runs again. I have to go over to another committee, unfortunately.

Senator NELSON. He would rather have you say something nice when it counts, I am sure.

Senator CASE. Well, I have this other committee and I have to do my duty there.

The committee has been examining Merck products in its hearings. Now I understand it is Merck's turn. I am glad that they asked for an opportunity to testify and that the committee found it possible to schedule them so soon after the other witnesses had testified. I am pleased to present these witnesses, representative of a company and an industry which occupy an important and valuable role in the life and growth of our State and our Nation.

Thank you very much, Mr. Chairman.

Senator NELSON. Thank you very much, Senator Case.

The committee is very pleased to have you appear here this morning and present these distinguished citizens from your State.

Senator CASE. Thank you.

Senator NELSON. How did you wish to proceed, gentlemen? You have a number of witnesses here. Do you have any particular schedule you want to follow?

#### INTRODUCTORY REMARKS OF HENRY W. GADSDEN, PRESIDENT, MERCK & CO., INC., RAHWAY, N.J.; ACCOMPANIED BY LLOYD N. CUTLER, SPECIAL COUNSEL, WASHINGTON, D.C.

Mr. GADSDEN. Mr. Chairman, I would like to make a few opening remarks and introduce Dr. Tishler, who will proceed to introduce Dr. Beyer, and then Dr. Lawrason, who did the clinical investigation. Then I shall return, as the final witness, to present a statement with reference to the company's marketing, advertising, and promotional activities, which, in our opinion, have fairly presented this drug and have positioned it appropriately in the minds of the physicians.

Shall I proceed?

Senator NELSON. Your biographical sketch will be printed at this point. Please proceed.

(The biographical sketch of Mr. Gadsden follows:)

#### BIOGRAPHICAL SKETCH OF HENRY W. GADSDEN, PRESIDENT, MERCK & CO., INC.

Henry W. Gadsden became president of Merck & Co., Inc., on January 15, 1965, after directing all the company's production, marketing, and research activities for nearly a decade as executive vice president.

Before becoming executive vice president and a director of Merck in 1955, he served as vice president and then administrative vice president. Mr. Gadsden had been a vice president and director of Sharp & Dohme, Incorporated, when the latter company merged with Merck in 1953.

Mr. Gadsden is a director of the Campbell Soup Company, New Jersey Bell Telephone Company, and the New Jersey State Chamber of Commerce. He is a member of the Board of Directors of the Pharmaceutical Manufacturers Association and secretary-treasurer and a director of the PMA Foundation. He is a trustee of the Committee for Economic Development; New Jersey State Safety Council, Inc.; and Seeing Eye, Inc.

Born in New York City April 16, 1911, Mr. Gadsden was graduated from Yale University in 1933, receiving a B.S. degree in economics. He was first associated with Bankers Trust Company in New York City (1933-34), and then with the management consulting firm of R. A. Lasley, Inc. (1934-37), also in New York. He joined Sharp & Dohme, in Philadelphia, in 1937.

At Sharp & Dohme, after two years as an analyst in sales research, Mr. Gadsden became assistant to the executive vice president in 1939; director of production and engineering in 1946; vice president in 1949; and a director in 1952.

During World War II, he served as executive officer of the Philadelphia Ordnance District of the U.S. Army, rising to lieutenant colonel. Returning to Sharp & Dohme in 1946, he served in a civilian advisory capacity as district chief of the Philadelphia Ordnance District from 1948 to 1955. He is a former vice president and director of the American Ordnance Association.

Mr. Gadsden formerly served as a director of the First Pennsylvania Banking and Trust Company; Provident Mutual Life Insurance Company; the Institute for Cancer Research, Philadelphia; and the Philadelphia branch of the American Cancer Society. He was formerly a trustee of Lankenau Hospital, Philadelphia; Overlook Hospital, Summit, N.J.; Episcopal Academy of Philadelphia; and Short Hills Country Day School.

A resident of Short Hills, New Jersey, Mr. Gadsden is married to the former Patricia Parker of Philadelphia. They have four sons: Christopher H., born in 1946; Thomas P., born in 1949; William F., born in 1955; and Robert W., born in 1956. The family formerly resided in Gladwyne, Pennsylvania, from 1949 to 1955.

**MR. GADSDEN.** Mr. Chairman, I wish first to express my appreciation and that of my associates for this opportunity to appear before the committee during the 5 days set aside for the examination of various aspects of indomethacin.

As you know, this drug was discovered by Merck scientists and is marketed by the company, for the management of certain arthritic disorders, under the trademark of "Indocid" abroad and "Indocin" in the United States.

We felt it urgently important that we present our testimony now, Mr. Chairman, because although the committee's intent may have been to focus on FDA actions relating to Indocin, the announcement of the hearings suggested a primary concern with the product and the behavior of our company.

The FDA has regulatory authority over all prescription drugs and a broad responsibility to protect the public interest as such drugs are developed, tested, and used. But, in practical terms, the agency cannot be held ultimately responsible for the safety and effectiveness of any specific drug product or for the integrity with which it is brought to the attention of physicians. In the final analysis, it is we who are responsible for both.

It is our purpose to present to the committee and place on the record our assessment of Indocin. In the process, we will also present a record of our performance.

With me today from the company are Dr. Max Tishler, president of our Merck Sharp & Dohme research laboratories; Dr. Karl H. Beyer, Jr., our senior vice president for research; and Dr. F. Douglas Lawra-

son, our vice president for medical affairs. You have statements of their background before you, as you have mine. Let me simply say that they are scientists whose research contributions and professional distinction are internationally recognized.

Also present with us today are two distinguished independent rheumatologists, who are prepared briefly and informally to discuss their own experience with Indocin and their own perception of its place in the management of arthritic disorders. I make this distinction, Mr. Chairman, because I want to emphasize the conditions under which they are here, lest these conditions be misunderstood.

To make the record absolutely clear: when we heard about this inquiry into Indocin and decided that we should ask for an opportunity to testify, we asked Dr. Smyth and Dr. Calabro if they would be willing to appear and use a few minutes of the time allocated to us. They have performed clinical investigations on Indocin under grants from Merck to defray the costs of the work. We offered to pay their expenses in coming to Washington. We are not paying them an honorarium for their appearance here. We would not and could not pay them for their testimony. We asked them to accompany us only because we believed it would be helpful to the committee to hear the views of practicing rheumatologists who have studied Indocin in patients.

We are also accompanied today by Mr. Lloyd Cutler as our Washington counsel.

As I said at the outset, I will submit a closing statement with reference to what we think is the very responsible conduct of the company in the presentation and positioning of the product.

May I now introduce the president of the Merck Sharp & Dohme research laboratories, Dr. Max Tishler, whose curriculum vitae is submitted for the record. He is recognized as one of the great industrial research directors in the Western World. Rather than summarize his long list of achievements and honors here and abroad, I shall mention only two. Dr. Tishler is a life trustee of Tufts University and a member of the National Academy of Sciences. Among its approximately 800 members, I understand the Academy has admitted less than 30 from industry. Dr. Tishler.

SENATOR NELSON. Doctor, the committee welcomes you and the other representatives of your distinguished company. We have always followed the policy on this committee, and I am sure we will continue to do so, which I have announced a number of times from the Chair, that we would permit any company from the drug industry to come before this committee upon its request. We desire to maintain a balance in the testimony, and I think at least a half dozen times from this chair, I have publicly invited both the companies and the Pharmaceutical Manufacturers Association to appear. So we welcome you here today.

I think I should say to you that you may have based some of your viewpoints about the hearings upon what you have read in some of the medical publications and trade press as well as on statements by the PMA, and you might very well have come to the conclusion that this committee has not intended to receive balanced testimony. In fact, as I read the statements going out in a fair percentage of the medical publications, those that are supported by advertising and those that are not, I do not recognize that I have attended the same hearings that these reports have covered. I say the same thing about the statements

I read coming from the association of which you are a member, the Pharmaceutical Manufacturers Association. So, I wish you to know that your company is welcome to come before this committee at your request at the earliest possible date we can schedule. That has been said repeatedly for every company in the country. I have, and I am sure the committee has no objection, made this statement because we intend to give to the industry an opportunity to respond to anything that is said at these hearings. We have made that position clear from the very beginning, and, as I understand it, your request to appear came a very short time ago and we scheduled it as you desired, forthwith. That has been our practice in the past and is our intent for all future hearings.

Senator Scorr. Mr. Chairman, may I congratulate the chairman on the promptness in which this company has been given an opportunity to reply to a good many statements, many of which are derogatory to it and some of which, I am sure from having looked over some of their statements, they are prepared to rebut.

I am aware that medical journals take one point of view on the matter and that the American press generally may be able to report only what it hears in this room and what the chairman or I or other members of the committee say. I do regret that there appears to be some effort to try this case in the press before it has been heard fully in the hearing room. I have not been entirely sympathetic to the position of the American Bar Association in its effort to inhibit the press in its reporting of crime news, but I think it is a crime in itself for the press to put any witnesses under a shadow before he testifies, and it is wrong to do this. I had read in a book once that you should never criticize the press, and I am now doing the worst thing that any politician should do, but I am doing it, I think, under this rather intensive provocation.

My criticism, however, is not directed as much to the press—and I hope they will give the same three-column treatment to your testimony as they gave to your opposition yesterday—but my criticism is fundamentally to the fact that the Food and Drug Administration, which often comes in to us to make recommendations, whom we listen to with a great deal of care, nevertheless seemed with altogether too much eagerness yesterday to have launched themselves into a series of attacks on this company, and the merits of this will develop as we hear all the testimony.

But I do not like the fact that Mr. Goodrich's testimony was so timed yesterday as to carry more than the implication of a threat in saying, as reported in the press, that decisions whether to recommend prosecution to the Justice Department now rests with him, the clear implication being that if you gentlemen and your company do not behave yourselves or if you give him too much trouble, you will pay for it. Dr. McCleery, as acting director of the FDA's Division of Medical Advertising, criticizes the advertising practices as seriously misleading. I am going to examine the entire testimony when we are through, with a particular eye on the credibility of Government witnesses and the motivation of Government witnesses and the timing of the appearance of Government witnesses for the purpose, apparently, of influencing or affecting the testimony of subsequent witnesses. I have been a member of the bar for more than 40 years, and I think I know slanted testimony when I see it. I think I know timing when I see it, and I

think I know the use of the press to create an impression before all the evidence is in when I see it.

I am glad to see that the press is making copious notes of this. I expect to be probably criticized in various columns as the tool of the interests, but after 26 years, I am able to bear that burden, also. I do not know any of you gentlemen, I never met you until this morning, and I am only interested in the fact that you shall have a fair opportunity to appear and to be heard. If you are wrong, I will condemn you just as cogently and incisively as my statement is critical of the apparent effort of a Government agency to gain a certain degree of publicity for its activities, a certain indecency, in my opinion, in rushing to the assault here where your testimony has not been heard. It might have been better if they waited to comment on your testimony.

I appreciate the chairman's giving me an opportunity to say this. Your drug may be a good drug, it may be a bad drug. It may cure or alleviate some of the arthritic disorders; it may not. I hope it will, because I have one of them. But right or wrong, I am pleading simply that, as the chairman has said, we have hearings fairly balanced—and he has been most careful here to see that you are properly brought in. But I plead for the same treatment in the press. I cannot expect it in the planted stories among the columnists, because we all do that. I cannot say non mea culpa. Every politician on the Hill is busy planting his views with some columnist; I have done it myself. So this is not said out of piety, but it is said out of recognition of the facts of life.

Recognizing these facts, I conclude simply by pleading once more for the most careful and fairest presentation of the testimony before the committee. As the chairman has so well demonstrated, he has concern for that. I also plead for the same kind of presentation in the press. I do not think that either Senators or newspapermen really know whether indomethacin is a good drug or not. So let us all join together, press and public and the Government, to find out whether the patient is receiving the kind of thoughtful care from the drug industry and from the medical profession, which we hope he is, which I personally believe he is, and let us keep the patient's concern in mind.

Thank you very much.

Senator NELSON. Thank you, Senator. I think I should comment on what the distinguished Senator from Pennsylvania has said.

One, as to the FDA rushing to the assault before the company has been heard, I would like to say that it is partly my fault. The FDA has not appeared before this committee at any hearing except at the request of the committee. We have requested the FDA to appear on specific problems. After having listened to all the FDA witnesses, having read their testimony very carefully before I came to the hearings and having talked to the witnesses, I think the testimony of these officials has been very carefully prepared and judiciously presented, in balance, and that they have presented their honest opinions. I must say they have been most persuasive in my listening to their testimony as well as listening to those who disagree with FDA. I have been tremendously impressed with the quality of the witnesses and the quality of their testimony.

In any event, they came at the request of the committee. We did not ask the Merck Co. to appear ahead of FDA and for the FDA to come to rebutt them. The purpose of the hearing is to learn about problems in the industry.

As to the press, given the fact that you conduct a 2- or 3- or 4-hour hearing covering very long and complicated testimony, and the fact that the reports of the press must necessarily be condensed because there is not that much space in the paper, I think that the press has done a balanced job of reporting. We have had a series of hearings here, the nature of which is to study what appear to be problems in the industry that are of public concern.

As to publicity of the industry, I do not think there is any doubt in the world that 99 $\frac{9}{100}$  percent of the inches in the press are favorable to the drug industry. There is only a tiny percentage that is unfavorable. That part that has been unfavorable with regard to drug pricing is unfavorable because it appears on its face to be an inexplicable pricing structure. We have heard from the industry in great detail, and I for one am not persuaded that it has given an adequate explanation of why a drug like prednisone should sell in competitive bidding in New York City, and to the Defense Supply Agency, and the Veterans' Administration, and hospitals for 45 cents a hundred and in the retail market for \$17.90 a hundred, while the Medical Letter, a distinguished publication, says that at least 22 versions of the drug with this vast price range are of equivalent therapeutic value.

This is a matter of important public concern. When you have two drugs of equal value, one selling for 45 cents a hundred to one group and the other for \$17.90 a hundred to pharmacists, that is news; and I would have considered the press quite biased if they had not printed it.

The other aspect that has been news is that the same company selling at \$17.90 to the pharmacists are themselves offering their drug in the competitive marketplace at \$1.20 a hundred; and at the same time, companies that are selling it for \$17.90 a hundred to the pharmacists in the retail marketplace in America are selling it for one-fourth that in the marketplace in Bern, Switzerland, and elsewhere. These are matters of news, and I do not think the press has been biased, frankly, in reporting this rather interesting and significant variance in the price structure.

**Senator SCOTT.** None of which I read in this morning's press, Mr. Chairman. I was not referring to that. I am not making any pre-judgment. I wonder if the fact that these witnesses are due to appear had anything to do with the fact that the only news in the paper this morning consists of attacks upon the witnesses before they have been heard. I would be doing less than my duty, even at the peril of a politician being critical of the press, if I did not say that I expect as a member of this committee a balanced reporting of what goes on here, and I think balanced reporting does not include an assault on the witnesses before they have been heard by quoting, after 4 hours of testimony, simply those statements which reflect on one company.

**Senator NELSON.** I would like to continue on this point. As to the FDA, I would want the Senator to know that there is no fault that rests with them. If there is any fault at all, it rests with the chairman of this subcommittee, because I decided upon the order in which they would appear.

**Senator SCOTT.** You did not write the story.

**Senator NELSON.** No, but I thought that perhaps you thought that the FDA volunteered to come in, as you put it, in the indecency to rush to the assault before the company was heard. I am only saying

that I was the one who requested them to appear on that day, and it does not reflect on the FDA.

I think you have a particular problem here. You have congressional committees which conduct hearings. They conduct hearings about problems that exist in the country, and it is these problems that the press report. If there are no problems in the industry, we do not expect the press to spend all its time on research to discover what the industry did that was good.

We had exactly the same situation when I introduced the first legislation for minimum tire safety standards and for uniform auto safety standards, both of which subsequently became part of the law of the land. I had people in my own State, where we have a very distinguished auto company, American Motors, and some distinguished tire companies who attacked me as being antiauto and antitire industry. I am not antiauto industry or antitire industry. I think they are great industries, just as the pharmaceutical manufacturing industry is a great industry and has made a great contribution to the country. But the fact was that there was something wrong in the industry and when the hearings were conducted, and the stories on the front page reported that there were defective and inadequate tires on the market, I think the press was right in reporting these facts. Everybody knows that the auto industry has made a great contribution to this country, but that does not mean that the auto industry is perfect, any more than the pharmaceutical manufacturing industry is perfect or the legal profession, of which I am a member, is perfect, or any other field is perfect.

The point that I make, and I do not think it has been made clear in the press and the drug industry, is that we are going to hear all viewpoints. We want to hear all viewpoints. We want a balanced record. We have been attacked by the Pharmaceutical Manufacturers Association for not hearing all viewpoints, I guess because you cannot hear all viewpoints at once. We have leaned over backward to tell the companies involved that they can testify any time they wish as soon as we can schedule a place and time. We have told the PMA the same, and it has come three times and has presented many witnesses. Other individual witnesses have to wait in line.

If the industry would prefer that they, either PMA or the companies, not have a preferential chance, which I think they are entitled to because we are talking about their business, the committee might very well proceed to listen to individual witnesses for the next 3 years, because we have had that many requests from individual doctors all over the country.

SENATOR SCOTT. Of course, if you tried that, you would have trouble with me, as you know.

SENATOR NELSON. My point is that we want balance and all viewpoints here. I say to you, representing the company, that if at any time in these hearings, you think there is a viewpoint that has not been heard from the industry standpoint, let the committee know and you will be heard. If I slip up on it, Senator Scott certainly will not. But I want that well understood from the beginning.

The other aspect I would like to mention is that whenever you conduct a hearing of this kind, members of the committee ask to explore the problem. The fact that you might cross-examine a witness or di-

rect-examine a witness or raise a tough question that sounds prejudicial does not mean anything at all. This is the way to explore an issue to get full information. If you have the information, the record will show the answer. This committee does not make medical judgments. We are trying to get the best professional witnesses we can find, and I think we have had some of the best in the country, as we intend to have, to conduct further hearings with the best witnesses we can find.

Mr. GADSDEN. Mr. Chairman, may I make a comment, please?

Senator NELSON. Surely.

Mr. GADSDEN. As will be evident in the subsequent testimony, while we disagree most deeply with some of the conclusions and statements of the Food and Drug Administration, we nevertheless, credit them with speaking out of sincere conviction. This is the way they saw it, but we do believe that they just happened to be in error as to their conclusions.

Senator NELSON. I think the FDA has very distinguished scientists and administrators and that they are sincere, just as I am sure you are. But that is the purpose of the hearing. If there is a difference in viewpoints, we want to hear yours so that, on balance, the record can be read and people can make a judgment about where the truth lies, whether it is on one side or the other or somewhere down the middle. We have had distinguished medical witnesses here—you are aware of this—from your own industry, from within the companies who will disagree vigorously about the interpretation of some kind of study, about the interpretation of the same set of facts. That is bound to be the case because medical science is still an art to a considerable degree. So there are bound to be differences of opinion. We want to hear all the best opinions we can get, both from those who feel one way and those who differ with them.

Mr. GADSDEN. Should Dr. Tishler proceed, sir?

Senator NELSON. I assume, Dr. Tishler, that if we have some questions while you are testifying, you will have no objection to interruptions?

**STATEMENT OF MAX TISHLER, PH. D., PRESIDENT, MERCK SHARP & DOHME RESEARCH LABORATORIES, DIVISION OF MERCK & CO., INC., RAHWAY, N.J.**

Dr. TISHLER. I have no objection.

Senator NELSON. We have your statement and your biographical data. They will both be included in full in the record. If there is something, while you are reading, that you would like to extemporize on or elaborate on that would have taken too much time to write out in detail, you may feel free to do so. If there is anything you would like to eliminate, feel free to do so, but your statement as submitted will go in the record in full, and anything you wish to change in the course of your testimony, you may.

Dr. TISHLER. Senator, I plan to read my statement.

(The biography of Dr. Tishler follows:)

**BIOGRAPHY OF MAX TISHLER, PH. D., PRESIDENT, MERCK SHARP & DOHME RESEARCH LABORATORIES DIVISION; MEMBER, BOARD OF DIRECTORS, MERCK & CO., INC., RAHWAY, N.J.**

Dr. Max Tishler, who heads the \$57-million-a-year research program of Merck & Co., Inc. is not only President of the Merck Sharp & Dohme Research Laboratories but also one of the nation's leading scientists in his own right.

When he was persuaded by the late George W. Merck to leave an academic career at Harvard to join the Merck laboratories, there were no antibiotics, no steroids, and only two vitamins commercially available. Dr. Tishler has contributed significantly in all of these and other fields of medicinal chemistry, having received more than 100 patents and published more than 100 papers. In 1953, he achieved national recognition with his election to the National Academy of Sciences.

In 1937, when Dr. Tishler became a member of the Merck research staff, it numbered fewer than 100 persons. Today he heads an organization totaling nearly 1,800, including representatives of some 35 diverse disciplines. (In addition, 500 persons are engaged in research and development in other divisions of Merck.) At major research centers in Rahway, N.J., and West Point, Pa., and several experimental farms, Dr. Tishler directs extensive research programs in human and animal health.

Major discoveries made in the Merck Sharp & Dohme Research Laboratories since Dr. Tishler assumed leadership in 1956 include drugs for the treatment of heart disease, hypertension, rheumatoid arthritis and other inflammatory diseases, and mental depression; and animal health products for control of economically significant diseases of poultry and livestock.

In addition to membership in the National Academy of Sciences, his honors include election to the American Academy of Arts and Sciences in 1965; the 1964 Chemistry Lecture Award of the Royal Swedish Academy of Engineering Sciences (Stockholm, Sweden); Rennebohm Lecturer, University of Wisconsin School of Pharmacy, (1963); the Julius W. Sturmer Memorial Lecture Award, Philadelphia College of Pharmacy, (1964); the 1963 Chemical Industry Award of the American Section of the Society of Chemical Industry; the 1961 Industrial Research Institute Medal; the 1960 Honor Scroll Award of the New Jersey chapter of the American Institute of Chemists; and the Merck Board of Directors Scientific Award (1951). He has received honorary D.Sc. degrees from Tufts University (1956), Bucknell University (1962), and the Philadelphia College of Pharmacy and Science (1966); and an honorary D.Eng. degree from Stevens Institute of Technology (1966). He is also a member of the honorary societies, Phi Beta Kappa and Sigma Xi. Funds from the Merck Board of Directors Award established the Annual Max Tishler Visiting Lectureship at Harvard and the Max Tishler Annual Scholarship at Tufts.

Born October 30, 1906, in Boston, Dr. Tishler was educated at Tufts University where he received his B.S. degree in chemistry, graduating magna cum laude. In 1929, he became Austin Teaching Fellow at Harvard University, and after receiving the degrees of M.S. in 1933 and Ph.D. in 1934, he became Research Associate with the late Professor Elmer P. Kohler, and in 1936, Instructor in Chemistry.

Joining Merck in 1937 as a research chemist, he served successively as Section Head of Process Research (1941-44) and Director of Developmental Research (1944-53). During this period, Dr. Tishler led the Merck teams which first synthesized hydrocortisone and developed commercial syntheses for vitamin B-2, pantothenic acid, and vitamin K-1. He also headed the development of production processes for penicillin, streptomycin, cortisone, and hydrocortisone.

His work in sulfa drugs included discovery of sulfاقinoloxaline, the first effective drug against coccidiosis, a costly disease of poultry, and he developed a number of practical syntheses of amino acids which furthered research in nutrition.

In collaboration with Dr. Selman A. Waksman, Rutgers' Nobel laureate, he isolated the first actinomycin in crystalline form. In recent years, related actinomycins have found use in the treatment of certain types of cancer. He also collaborated with Dr. Waksman on a book entitled *Streptomycin*, and with Harvard's Dr. James B. Conant on *Chemistry of Organic Compounds*, a textbook.

In 1954, he became Vice President for Scientific Activities, and in 1956 was

named to head the Merck Sharp & Dohme Research Laboratories as Vice President and Executive Director, being named President in 1957. He was elected to the Board of Directors of Merck & Co., Inc. in 1962.

Dr. Tishler is active in educational affairs and serves on a number of scientific advisory committees affiliated with the U.S. government, with the numerous professional societies of which he is a member, and with the pharmaceutical industry.

Dr. Tishler and Mrs. Tishler, the former Elizabeth M. Verveer, reside in Westfield, New Jersey, and are the parents of two sons, Peter Verveer and Carl Lewis.

#### CURRENT AFFILIATIONS (UNLESS OTHERWISE NOTED)

##### *Civic*

National Research Council of the National Academy of Sciences: Member, Advisory Committee on Tropical Medicine; member, Committee on Role of Patents in Research.

##### *Educational*

Columbia University: Member, Scientific Advisory Committee, International Institute for the Study of Human Reproduction.

Harvard University: Member, Visiting Committee (School of Public Health); member, Visiting Committee (Department of Chemistry).

University of Pennsylvania: Associate Trustee (Science); member, Physical and Biological Sciences Board.

Rutgers University: Member, Advisory Committee, School of Medicine.

Tufts University: Life Trustee; member, Executive Committee; vice chairman, Educational Policy Committee; member, Development Committee of Board; consultant, Modernization of Chemistry Department; member, Administrative Board, Tufts-New England Medical Center; chairman, Visiting Committee (Chemistry); member, Board of Advisors, School of Dental Medicine Program.

Union Junior College: Trustee.

The Fund for Overseas Research Grants and Education: Member, Board of Directors.

The Weizmann Institute of Science: Member, Board of Governors.

##### *Industry*

Industrial Research Institute: Member, Advisory Editorial Board, "Research Management"; former member, Board of Directors (1962); member Awards Committee.

Pharmaceutical Manufacturers Association: Member Research and Development Section.

##### *Professional*

Agricultural Chemical Society of Japan: Member.

American Association for the Advancement of Science: Fellow.

American Chemical Society: Member; former chairman, Organic Chemistry Division (1953-54); former councillor, North Jersey Section; member, Committee to Study Chemistry in Industry (Project of Committee on Chemistry and Public Affairs).

American Institute of Chemists: Fellow; former councillor (1959-61).

Association of Harvard Chemists: Member; past president (1964).

"Chemical & Engineering News": Member, Advisory Board.

Chemical Society (London): Fellow.

Chemical Society of Japan: Member.

Directors of Industrial Research: Member.

New York Academy of Sciences: Fellow.

"Organic Syntheses": Former member, Editorial Board (1954-59); former Editor-in-Chief (1959).

"Separation Science": Member, Board of Editors.

"Industrial Research": Member, Editorial Advisory Board.

Society of Chemical Industry: Honorary Vice-President (1968-69); member, Executive Committee (1963-68); former Chairman (1966), American Section; Chairman, Nominations Committee (1968).

Swiss Chemical Society: Member.

Dr. TISHLER. My scientific colleagues and I welcome and appreciate the opportunity to tell this committee about the development and introduction of indomethacin. You will forgive me, Mr. Chairman,

if I talk about the Merck Sharp & Dohme research laboratories with pride. But it is pride in others: in the achievements of my fellow scientists, and in the consistent philosophy of a management that believes that the two most important ingredients of research are quality and integrity.

The pharmaceutical industry laboratory, Mr. Chairman, is organized to bring together scientists of widely different disciplines, all needed to carry a program from the conceptual stage through clinical investigation. They comprise men from at least 35 separate disciplines—from chemists to pharmacologists, pathologists, biologists, physicists, engineers, and physicians, who are joined together to seek solutions to medical problems. In our society, pharmaceutical research laboratories have almost unrivaled capacity for such collaborative research in medicine.

This is the way our laboratories are organized at Merck, which considers research to be the vital heart of the company. To the best of our knowledge, there is no sizable company outside the pharmaceutical industry that over the years spends a higher percentage of its own revenues—excluding government support—for research and development.

Our budget for this work is the largest published of any pharmaceutical concern in the free world—\$57 million this year, of which less than 2 percent comes from government. We have 2,300 people engaged in this work, of whom more than 500 have advanced academic degrees. Last year they published nearly 150 research papers in scientific journals.

Senator NELSON. Are you saying that \$57 million is the figure that you identify as a cost accounting factor for research in your company?

Dr. TISHLER. Yes, it is.

Senator NELSON. Some times we have had trouble trying to get figures on how much is research, because company officials say it is difficult to separate it out, and I suppose it is.

Mr. GADSDEN. I am not aware of your previous discussion on this point, Senator. I would assume that perhaps the problem had to do with the cost accounting principles of allocation to a specific project. However, under our system, we can tell you how much is spent for research throughout the company, and this is the figure to which Dr. Tishler is referring.

Senator NELSON. When you refer to 2,300 people engaged in this work, just so I have it clear in my mind, I am not sure how you distinguish research from something else, but does this involve quality control, too?

Dr. TISHLER. No, this does not involve quality control. If you would like a breakdown on the type of research I am referring to, we have exploratory research, fundamental research, basic research, developmental research, and applied research—five categories of research. It is broken down into these categories. Most of the research is directed toward investigating, searching for new therapeutic agents, trying to find the limitations and scope of therapeutic drugs, developing the processes to make the products, doing all the physical things that are part of the controls that we have to set up for the situation.

Senator NELSON. You have refined these categories a bit since I have been in school. It was pure and applied research in those days.

**Dr. TISHLER.** We have good reasons for breaking it into five categories.

**Senator NELSON.** I am sure you do.

**Mr. GADSDEN.** I would have to tell you that this is Merck terminology, and what this means to us may not be the same as what it might mean in another research establishment.

**Dr. TISHLER.** That is correct.

Shall I proceed?

**Senator NELSON.** Please go ahead.

**Dr. TISHLER.** It is the quality and integrity of research that counts, not its quantity. To illustrate this point, it would be relevant, I believe, to give the committee a brief description of how Merck got into the long and difficult war against rheumatoid arthritis, a war in which indomethacin is one more significant advance.

Thirty-five years ago, a few years before I came to the company, hardly more than a young lecturer from the Harvard Chemistry Department, some Merck scientists became interested in helping to isolate the active ingredient of the yellowish outside layer, or cortex, of the adrenals—those two tiny glands that sit on top of each kidney. An insufficiency of this ingredient—even then thought to be a steroid hormone—causes Addison's disease, a normally fatal illness.

What was the basis for Merck's interest in this field? There was little or no commercial reward at the end of the road. Only 800 Americans were then known to have Addison's disease, and they were kept quite healthy on adrenal extracts. The only possible reward for the effort appeared then to be scientific and medical. The active ingredient of the adrenal cortex was believed to be vital to life. My colleagues were not looking for a commercial drug to cure a specific disease. They were chiefly seeking knowledge to cure ignorance, which is the greatest enemy of human health.

If this seems sententious, it is also practical. In 1933, when George Merck established the pioneer laboratory in our industry, he was persuaded that the long-range success of both our research and the company itself would depend primarily on our ability to make fundamental and lasting contributions to human health. This has been our philosophy and our practice ever since.

It took more than a decade of failures, however, to synthesize cortisone, which had been isolated earlier from the adrenal cortex. The first complete synthesis was achieved in 1944 by a 26-year-old Merck chemist, Dr. Lewis H. Sarett, who had come to us from Princeton 2 years before. Four more years were required to produce enough cortisone to try it in Addison's disease. It was successful for this use, but there was little interest on the part of clinical investigators in exploring uses in other diseases.

Then came the historic letter from Dr. Philip Hench, the great rheumatologist of the Mayo Clinic, explaining a scientific hunch and asking for some of this scarce chemical to try on a carefully studied bedridden rheumatoid arthritis patient. We sent Dr. Hench a single gram of cortisone for his patient. On September 28, 1948, a few days after treatment started, the patient rose from her bed and walked out of the clinic. From his scientific hunch, from one gram of cortisone and one well-studied patient, Dr. Hench made the epic discovery that won him the Nobel Prize.

Several years after he made medical history by using cortisone in rheumatoid arthritis, Dr. Hench told a Senate committee:

The work of investigators in scientific research is different from that in any other field that I know of. Frequently they are dealing with ideas for which there are no words. Thoughts are chemical processes, and there are times when a chemical process can be felt without any appropriate words.

So that the only way you can really judge the quality of the members of any research organization is, in my opinion, by what they do—by their fruits.

Dr. Hench was referring to our laboratories. Some of what my colleagues there have done is told in a booklet, "By Their Fruits," which I would like, Mr. Chairman, to submit for the record.<sup>1</sup>

Senator NELSON. Yes, it will be received.

Mr. GADSDEN. Is this the appropriate way?

Senator NELSON. Just leave it at the desk here.

Senator SCOTT. Mr. Chairman, I have to leave for the time being. May I have your permission to submit a statement at the end of the testimony if I decide to do it?

Senator NELSON. Yes, it will be printed in the record.<sup>2</sup>

Senator SCOTT. I shall try to get back.

Senator NELSON. Thank you, Senator.

Please proceed, Dr. Tishler.

Dr. TISHLER. This booklet I submitted, Mr. Chairman, describes the contributions, up through 1963, of our company's scientists to some of the landmarks in chemical medicine.

These accomplishments have become part of medical history, but let me remind you that in 1933, while I was still a graduate student at Harvard—and this was not so long ago—there were no vitamins; no sulfas; no antibiotics; no antihypertensives; no antidepressants; no corticosteroids; no polio, measles, or mumps shots; no blood plasma; no anticoagulant therapy; no controllers of gout; and no broadly effective diuretics. Today, these words are part of the layman's language and the tools of our physicians. The work of Merck scientists played a key role in progress in the research and development in these fields.

Therapy in these fields has had an impact on the world around us. Anyone who has been a member of the Merck scientific team during any part of this period is proud of our contributions to these advances which have helped to wipe out or reduce the terror of whole categories of disease and have contributed dramatically to the extension of man's lifespan \* \* \* a gift of years that has been called the greatest technological achievement of the 20th century.

One of the drugs of which my colleagues and I are most proud is indomethacin. It is recognized by our peers in the world of science and medicine as a creative masterpiece. At least a hundred first-rate, technically trained men and women in more than 20 different disciplines at Merck made contributions to this research and development achievement over a period of a decade. They have been rewarded in the only way that counts. Upward of a million people have been able, as a result of indomethacin, to lead happier, more productive, and less painful lives. This is what research at Merck is all about.

<sup>1</sup> Retained in committee files.

<sup>2</sup> See statement, p. 3451, infra.

In 1959, Mr. Chairman, an attempt was made to measure the contributions of industrial laboratories to the growth of fundamental knowledge. A study of the basic research articles printed in scientific journals during the course of 1 year was published in the weekly magazine, *Science*. Merck stood fifth on the list, right behind General Electric, Bell Telephone, Du Pont, and American Cyanamid. They averaged a third more papers than did we, but they also averaged over 30 times our financial resources.

But if my colleagues have reason for pride, they also have reason for discouragement. I am not referring only to disparagement of our work, though this is sometimes heartbreaking. I am referring to the painful slowness with which we and our counterparts in other pharmaceutical laboratories and our collaborators in the great research organizations of government, universities, and medical schools around the world are able to push back the frontiers of ignorance.

For most illness, such as the degenerative diseases, we have not yet found either the cause or the cure. While we can discover drugs like indomethacin which improve the health and well-being of patients, we are still fighting our way through the dark, and we are often terribly discouraged.

Biomedical knowledge is almost half a century behind that of the physical sciences in the accumulation of knowledge of the kind and depth that leads to major discoveries. The situation stems from the complexity of life. In the human body research is dealing with something like 100,000 or more biochemical processes. When you add to this the tremendous genetic complexities of the human being, the most complicated hybrid on this planet, you can see how difficult it is to make a statistical analysis of his chemical and emotional reactions. The number of unknown variables with which we have to cope is well beyond our present comprehension. We still can and do make significant progress, but it is clear that if research is really to conquer disease, we must never lose sight of our central task: the accumulation of more and more basic knowledge. This will require patience on the part of all, including the Congress, which has been so generous in recent years with appropriations for basic research in medicine.

Turning again to rheumatoid arthritis: in few other fields of medicine is our basic knowledge more deficient than it is in rheumatoid arthritis. Though indomethacin has given relief to many patients who suffer from this disease, there is still a deep dissatisfaction connected with this achievement. It is a dissatisfaction, too, for the medical profession and for the millions of victims of rheumatoid arthritis and related diseases. Neither we nor anybody else has found either the cure, or for that matter, the cause or causes of these diseases. All we have discovered are better ways to relieve painful suffering and return invalids to productive lives. This is important. But we still have before us the challenge to finish the job—namely, to cure and prevent the diseases themselves.

We now want to concentrate on the specific stage of our long research effort in this field—that of indomethacin—that now interests you and your committee. To tell you about this program, I would like to call on Dr. Karl Beyer, Jr., senior vice president for research of our laboratories. He is a distinguished scientist with an international reputation. He has both an M.D. degree, and a Ph. D. degree in physiology. He is a past president of the American Society for Pharmacology and

Experimental Therapeutics, which in its 60 years has honored only one other scientist from industry with this post. He is a member of the Drug Research Board of the National Academy of Sciences, and among his other honors will be the Distinguished Service Award of the University of Wisconsin, which he will be awarded in Madison 2 weeks from today.

Thank you very much.

Senator NELSON. Thank you very much, Dr. Tishler. We appreciated having your testimony.

We shall be pleased to hear from Dr. Karl Beyer, and we are pleased that my alma mater has seen fit to honor you with a distinguished service award, which is eloquent testimony to your qualifications.

Dr. BEYER. Thank you, sir.

Senator NELSON. Dr. Beyer, we have your biography and statement, both of which will appear in the record in full. You may proceed in any way you wish.

(The biographical data of Dr. Beyer follows:)

**BIOGRAPHY OF KARL H. BEYER, JR., M.D., PH. D., MERCK SHARP & DOHME RESEARCH LABORATORIES, WEST POINT, PA.**

**GENERAL INFORMATION**

Born June 19, 1914, Henderson, Kentucky; married; two daughters.

**SPECIALIZATION**

Pharmacologist and Physiologist, with principal research interest being in the fields of renal pharmacology, metabolism of drugs in the body and enzymologic studies on secretory mechanisms of cells.

**EDUCATIONAL RECORD**

B.S.—1935: Western Kentucky State College.

Ph.M.—1937: University of Wisconsin.

Ph. D. in Physiology—1940: University of Wisconsin.

M.D.—1943: University of Wisconsin.

**CAREER SUMMARY**

Instructor in Chemistry: Western Kentucky State College, 1935–36.

Instructor in Physiology: University of Wisconsin Medical School, 1939–43.

Assistant Director of Pharmacological Research, Sharp & Dohme, 1943–44.

Director of Pharmacological Research, Sharp & Dohme, 1944–50.

Assistant Director of Research, Sharp & Dohme, 1950–56.

Director of Merck Institute for Therapeutic Research, West Point, Pa. 1956–58.

President of Merck Institute for Therapeutic Research, 1961–66.

Vice President for Life Sciences, Merck Sharp & Dohme Research Labs., West Point, Pa., 1958–66.

Senior Vice President, Research—Merck Sharp & Dohme Research Labs., West Point, Pa., 1966–.

**MEMBERSHIPS**

Fellow in the American College of Physicians (F.A.C.P.).

Fellow in American Association for Advancement of Science.

Fellow in The New York Academy of Sciences.

Fellow in The Royal Society of Medicine.

Member of the American Chemical Society; American Physiological Society; Society for Experimental Biology & Medicine; Philadelphia Medical Society; Philadelphia Physiological Society; American Society for Pharmacology & Experimental Therapeutics (Secretary, 1959–61; President, 1964–65; Past-President, 1965–66); Federation of American Societies for Experimental Biology (President, 1965–66); Canadian Pharmacological Society; Association of American Medical Colleges; The American Therapeutic Society; Society of Toxicology; Amer-

ican Society of Nephrology; Council on Circulation & Renal Section, American Heart Association; International Society for Biochemical Pharmacology; Board of Trustees, Biological Abstracts (Treasurer, 1965- ); Drug Research Board, National Academy of Sciences, 1964- ; Editorial Committee, Annual Review of Pharmacology; Editorial Board, Journal of Clinical Pharmacology & Experimental Therapeutics; Committee on Biological Handbooks; National Society for Medical Research Board, 1964- ; Who's Who in America; The Newcomen Society in North America.

## AWARDS

The Merck Scientific Award (1959).

The Gairdner Foundation Award (1964).

Modern Pioneers in Creative Industry Award, Natl. Assoc. of Mfrs. (1965).

Modern Medicine's Award for Distinguished Achievement (1967).

American Pharmaceutical Association's Foundation Award in Pharmacodynamics (1967).

## OTHER AFFILIATIONS

Lecturer in Physiology: Jefferson Medical College.

Lecturer in Pharmacology: Temple University Medical School.

Lecturer in Pharmacology: Graduate Medical School, University of Pennsylvania.

Special Lecturer in Pharmacology: Woman's Medical College.

## PUBLICATIONS (OVER 150 PUBLICATIONS, INCLUDING THESE LISTED)

"Sympathomimetic Amines: The Relation of Structure to Their Action and Inactivation" (Physiol. Rev. 26: 169, 1946).

"Functional Characteristics of Renal Transport Mechanisms" (Pharmacol. Rev. 2: 227, 1950).

"Pharmacological Basis of Penicillin Therapy" (Chas. C. Thomas, Publisher, Springfield, Ill., 1950).

"Factors Basic to the Development of Useful Inhibitors of Renal Transport Mechanisms" (Arch. Int. Pharmacod., 98: 97-117 (May) 1954).

"The Mechanism of Action of Chlorothiazide" (Ann. N.Y. Acad. Sci., 71: 363, 1958).

"Newer Diuretics in Progress of Drug Research" (E. Jucker, Ed., Basle, 2, pp. 9-69, 1960).

"Effect of Drugs on Active Transport", in "Enzymes & Drug Action" (Ciba Foundation Symposium, 1962. Ed. J. L. Mongar and A. V. S. deReuck; Pub. by J. & A. Churchill Ltd., London, England.)

"Physiological Basis for the Action of Newer Diuretic Agents" (Pharmacol. Rev. 13: 517-562 (Dec.) 1961).

"Fetal Malformations" (Arch. Env. Health 5: 94-96, 1962).

"The Effect of the New FDA Regulations on the Drug Industry" (Clin. Pharmacol. Therap. 5: 1-5, Jan.-Feb., 1964).

"Method of Inhibiting Gastro-Intestinal Irritation" Patent No. 3,129,137 dated Apr. 14, 1964.

"My Criteria for Acceptable Research in Pharmacology" (Am. J. Pharmaceutical Education 28: No. 5, Dec., 1964).

"Renotropic Characteristics of Ethacrynic Acid; A Phenoxyacetic Saluretic-Diuretic Agent" (J. Pharmacol. Exp. Ther. 147: 1-22, 1965).

"From Theory to Therapy" (Proc. Western Pharmacol. Soc. 8, 1965).

"Perspectives in Toxicology" (Toxicol. & Appli. Pharmacol. 8: No. 1, Jan., 1966).

"The Federation in Midpassage", Introductory Remarks. Fed. Proc. 25: No. 5. Sept.-Oct. 1966.

**STATEMENT OF KARL H. BEYER, JR., M.D., PH. D., SENIOR VICE PRESIDENT FOR RESEARCH, MERCK SHARP & DOHME RESEARCH LABORATORIES, DIVISION OF MERCK & CO., INC., RAHWAY, N.J.**

Dr. BEYER. Thank you, Senator.

As has been stated by Dr. Tishler, neither the cure for nor the etiology of rheumatoid arthritis is yet within the realm of knowledge of physicians and medical scientists.

However, the development of a multitude of useful medicinal agents over the past 20 years—some of them, like indomethacin, for disease entities still beyond our capability for understanding—provides evidence that one does not need to know all about a biological function to alter it beneficially.

The development of indomethacin does not suggest that we have moved any closer to understanding the factors that precipitate or are involved in the rheumatoid process. What the successful application of the compound does imply is that, with the benefit of accrued knowledge and experience, Merck scientists were able to formulate a working hypothesis as to what initiated and sustained the inflammatory process; and also able to develop methodologies for the discrete examination in laboratory animals of the effects of candidate compounds on the basic factors of the disease.

While the search for more potent corticosteroids continued in the early 1950's, a group of Merck scientists and biochemists started what was to be a 12-year search in another direction—to find a compound that was not hormonal in nature, but that would still provide the benefits of the steriods.

Early in 1957 the attention of the scientists in this program turned to compounds with an indole nucleus. This was because an indole metabolite, serotonin, was thought to play a role in initiating and sustaining inflammation. A number of serotonin antagonists were synthesized by Merck chemists and made available for pharmacologic assessment as anti-inflammatory agents.

The serotonin theory eventually proved to be wrong, but it did provide the first promising chemical lead in our nonsteroid program.

The program began to achieve full focus later in 1957, when Merck scientists observed the first promising indole derivative after evaluating hundreds of unsuccessful agents, but it did not live up to the expectation of Merck scientists and physicians and was dropped.

In March 1961, another promising derivative was finally synthesized. That compound, too, was effective in preclinical studies, but even as clinical trials were being planned, our scientists developed another indole derivative, indomethacin, which appeared to have greater potency with less toxicity than any of the previous compounds.

Before indomethacin could be studied in man, it had to undergo lengthy and comprehensive testing in animals. More than 100,000 animals were used during the nonsteroid anti-inflammatory program leading to the development of the compound.

While animals themselves do not suffer from rheumatoid arthritis as a disease entity, we have been able to utilize a number of animal models to define, reproduce, and control in the laboratory fundamental phenomena involved in arthritic diseases.

Through the capability of developing methodologies for the control of biological phenomena in animals, our pharmacologists achieved the ability to strip arthritis down to its essential elements of inflammation, swelling, pain, and heat or fever, so that the action of potential compounds could be examined unfettered by the imponderables created clinically as patient, disease, and drug interact.

Some examples of animal models to test for antiarthritic activity are the carrageenin assay, which helps in the assessment of a drug's ability to reduce inflammation, pain, and swelling; the granuloma cot-

ton pellet assay, for measuring a drug's ability to inhibit inflammation and fibroblast proliferation; and still other tests which provide an indication of the analgesic and anti-inflammatory properties of compounds.

Additional control of these animal models is afforded by a comparison of the dosage of the drug with the response. Moreover, such dosage-response relationships are further compared with those of compounds commonly employed in the management of arthritic disorders. These comparisons are more than comparisons of potency, for we are able to compare the qualitative characteristics of the compounds as well.

The sizable and comprehensive animal studies with indomethacin provided clinicians with demonstrative evidence of the safety and efficacy of the compound, warranting tests in man.

The anti-inflammatory activity of indomethacin was demonstrated in the cotton pellet granuloma inhibition test in mice in which granuloma inhibition was observed following both oral and local administration. It was also demonstrated in the inhibition of edema induced by injection of the irritant, carrageenin, into the hind paw of rats.

Fever-reducing activity was demonstrated by inhibiting the fever produced by injection of a bacterial endotoxin in both rabbits and rats, as well as yeast-induced fever in rats.

In these and other tests, the potency of indomethacin was significantly greater than that of the anti-inflammatory compounds with which it was compared. It must be noted, however, that these studies comparing indomethacin with other known compounds, though serving as valuable indicators to the clinical investigator, are based on phenomena measured in animals and are not directly translatable to disease in man.

As part of the pharmacologic assessment, indomethacin was examined in the laboratory for its effect on the heart, the cardiovascular system, and autonomic reflex mechanisms, as well as for its effect on excretion, renal function, and animal behavior. Indomethacin did not affect any of these organ systems and processes.

When methodology was needed to examine a specific effect, we devised it if it was not available. Just as the Porter-Silber test, for example, bearing the name of two members of our staff, has become standard procedure in steroid measurement, so we devised new methodology to enhance reliability of metabolic studies with indomethacin. To do this required meticulous knowledge of the physiology of the animals employed in the studies and the synthesis of indomethacin compounds labeled with radioactive carbon. Such advances in methodology not only furthered our own indomethacin studies, but also contributed to the studies of scientists in other laboratories, since much of our methodology was published in detail.

Tests in several species to determine the metabolic fate of indomethacin indicated that in the dog, the drug present in the plasma is essentially all unchanged indomethacin. In other animals, metabolism of the drug differs. In the guinea pig, a significant amount of the drug is present in the plasma as a metabolite, with a small amount of indomethacin present in the cerebrospinal fluid. The route of excretion depended on the species and not the dose or the route of administration.

The influence of indomethacin and hydrocortisone on resistance to

infection was studied extensively in mice, rats, and rabbits, both before and subsequent to the initiation of clinical trials.

In the area of bacterial infection, in investigations in mice and rats, 10 different bacterial pathogenic microorganisms were used and the drug was given at several dose levels and treatment schedules. In contrast to hydrocortisone, indomethacin produced no detrimental effects in any of the experimental infections, even when administered in amounts 80 to 330 times the threshold dose for anti-inflammatory activity.

In the area of viral infection, indomethacin neither increased nor decreased resistance, in mice, to infections induced by the influenza A, Columbia SK, or the Eastern Equine encephalomyelitis virus.

In contrast to the adrenal corticosteroids, indomethacin did not depress antibody formation, which is a defense mechanism of the body against infection. These findings undoubtedly accounted, in part, for the contrasting effects of indomethacin and hydrocortisone on experimental bacterial infections, as mentioned above.

Taking all observations into account, it was held to be most probable that indomethacin would have no effect, beneficial or detrimental, on infections in man.

The safety assessment of indomethacin in the laboratory has been the most extensive we have ever undertaken and has included acute, subacute, and chronic toxicity studies in mice, rats, guinea pigs, rabbits, cats, dogs, monkeys, domestic pigs, and chickens. Chronic toxicity studies were continued for 26, 52, and 129 weeks in dogs; 35, 57, and 80 weeks in rats; 18 weeks in monkeys; 22 weeks in rabbits; and 27 weeks in guinea pigs. Acute and subacute toxicity studies were conducted in mice, cats, domestic pigs, and chickens. Reproduction studies included two-generation tests in mice, the recommended two-litter study in rats, and an established pregnancy test in rabbits.

The only toxicity that could be clearly identified as a direct effect of indomethacin was the production of gastrointestinal lesions of the type reported in animals for aspirin, phenylbutazone, and the anti-inflammatory steroids. Where anti-inflammatory potency and gastrointestinal irritation could be tested in the same species, the therapeutic ratio was as favorable for indomethacin as for phenylbutazone or the steroids. This type of potential side effect of antiarthritic dosages of aspirin, phenylbutazone, and steroids is well known to the physician.

Of course, there were other side effects we could not foresee which have occurred in man, but they were primarily of the subjective, sensory type, such as headache and dizziness, which are not usually observed in animals, since animals cannot communicate with man.

In the interest of time, I should like simply to condense the rest to say that the publications from our laboratories clearly disclose the results of the extensive animal studies carried on in the preclinical evaluation of indomethacin. They have not been challenged, even in the face of intensive investigation of the compound by other scientists.

The details of these studies are found in an extensive monograph which was provided each investigator and the FDA before clinical studies were undertaken. Reports of animal data to FDA and investigators were updated regularly to reflect the findings of animal studies continuing after the preclinical phase had been completed and the human studies were underway.

No drug, to my knowledge, has received a more intensive preclinical assessment than indomethacin. Except for the sensory effects, the transposition of the total preclinical assessment to experience in man has been gratifying.

The critical clinical evaluation phase, and the professional review period following the discovery of a new drug, will be covered by my colleague, Dr. F. Douglas Lawrason, a certified member of the American Board of Internal Medicine, and former dean of the University of Arkansas School of Medicine.

May I introduce Dr. Lawrason?

**Senator NELSON.** Thank you very much, Dr. Beyer, for your very valuable contribution to the discussion of this drug. As I think you perhaps know, I believe all of the witnesses, including the FDA, have commented upon the value of the drug in the treatment of rheumatoid arthritis and some other conditions. What they have differed on is the interpretation of some of the tests that have been made and the place that Indocin has in the medical armamentarium.

But if my memory is correct, there has not been any question in anybody's mind that it has a useful and valuable place in the treatment of rheumatoid arthritis and some other related conditions.

Thank you very much.

**Dr. BEYER.** Thank you, sir.

#### STATEMENT OF F. DOUGLAS LAWRAZON, M.D., VICE PRESIDENT FOR MEDICAL AFFAIRS, MERCK SHARP & DOHME RESEARCH LABORATORIES, DIVISION OF MERCK & CO., INC., RAHWAY, N.J.

**Senator NELSON.** Dr. Lawrason, the committee appreciates having you here today. You did submit, I think, a biographical sketch.

**Dr. LAWRAZON.** That is correct.

**Senator NELSON.** Your full statement and biographical sketch will be printed as supplied to the committee by you. You may proceed to give your testimony as you see fit.

(The biography of Dr. Lawrason follows:)

#### CURRICULUM VITAE

##### I. Name : F. Douglas Lawrason, M.D.

##### II. Education :

University of Chicago, 1937-40.

University of Minnesota, B.A., 1941.

University of Minnesota Graduate School, M.A., 1944.

University of Minnesota School of Medicine M.D., 1944.

##### III. Internship and Postgraduate Training :

Yale School of Medicine.

New Haven Hospital, New Haven, Conn., Internship and Residency, 1944-48.

##### IV. Teaching or Research Experience :

University of Minnesota, Assistant in Anatomy, 1942-44.

Yale School of Medicine, Dept. of Internal Med. James Hudson Brown Memorial Res. Fellow, 1949.

Yale School of Medicine, Dept. of Internal Med., Instructor in Medicine, 1950.

Yale School of Medicine, Dept. of Internal Med., Assistant Professor, 1951.

National Academy of Sciences, Washington, D.C., National Res. Council, Div. of Med. Sciences, Professional Associate, 1950-53.

Univ. of North Carolina School of Medicine, Chapel Hill, N.C., Asst. Prof. of Med. and Asst. Dean, 1953-55.

Univ. of Arkansas Medical Center, Little Rock, Ark., Prof. of Med., Provost for Medical Affairs and Dean of the School of Medicine, 1955-61. Merck Sharp & Dohme Research Laboratories, West Point, Pa., 1961 to present.

Research studies included—

Research concerned with cancer and leukemia in inbred strains of mice, at the University of Minnesota.

Investigation of new methods for the determination of plasma proteins and investigation concerned with salt and water excretion as related to renal dynamics, at the Yale School of Medicine.

Studies in experimental leukemia in inbred mice with particular reference to immunologic aspects and factors of resistance of transplanted tumors, at the University of North Carolina School of Medicine.

As a United States Naval Reserve Officer, studies in experimental anemia in swine, hematologic studies in animals exposed to atom bomb radiation (Bikini) and hematologic follow-up studies in Japanese exposed to atomic bomb; done at the Philadelphia Naval Hospital and the Naval Medical Research Institute, Bethesda, Md.

V. Medical Practice:

Medical practice associated with various professional appointments listed.

VI. Medical Publications:

Lawrason, F. D. Studies of Leukemia and Mammary Cancer in Inbred Mice. Thesis for M.A. University of Minnesota, 1944.

Kirschbaum, A., Lawrason, F. D., Kaplan, H. S., and Bittner J. J. Influence of Breeding on Induction of Mammary Cancer with Methylcholanthrene in Strain Dba Female Mice, Proceedings of the Society for Experimental Biology & Medicine 55:141, 1944.

Lawrason, F. D., Kirschbaum, A. Dietary Fat with Reference to the Spontaneous Appearance and Induction of Leukemia in Mice. Proceedings of the Society for Experimental Biology & Medicine 56:6, 1944.

Lawrason, F. D. and Cronkite, E. P. Incidental Finding of Megaloblastic-like Cells in Bone Barrow of One of Two Swine with Macrocytic Anemia and Chlorhydrin. Yale Journal of Biology & Medicine 29:87, 1949.

Lawrason, F. D., Eltzholz, A. C., Sipe, C. R., and Schork, P. K. Correlation between the Mean Corpuscular Volume and Reticulocytosis in Phenylhydrazine Anemia in Swine. Blood 4:1256, 1949.

Goodyer, A. V. N., Relman, A. S., Lawrason, F. D., Epstein, F. H. Salt Retention in Cirrhosis of the Liver. Journal of Clinical Investigation 29:973, 1950.

Epstein, F. H., Lawrason, F. D., Relman, A. S., Goodyer, A. V. N. Studies in Salt Excretion during Quiet Standing. Journal of Clinical Investigation 30:63, 1951.

Erslov, A. J., Iverson, C. K., and Lawrason, F. D. Cortisone and ACTH in Hypoplastic Anemia. Yale Journal of Biology & Medicine 25:44, 1952

Wagner, R. and Lawrason, F. D. The Production of Fever by Influenza Viruses. IV. Effects of ACTH and Cortisone.

Lawrason, F. D., Alpert, E., Mohr, F. L., and McMahon, F. G. Ulcerative-Obstructive Lesions of the Small Intestine. Journal of the American Medical Association 19:641-44, 1965

VII. Present position:

Vice President for Medical Affairs, Merck, Sharp & Dohme Research Laboratories, West Point, Pa.

**Dr. LAWRSOON.** Mr. Chairman, members of the committee:

My major responsibility is the clinical investigation of Merck drugs, as a member of a team of 40 physicians who are devoting their careers to this work. The clinical investigation of indomethacin has been my responsibility.

In this statement, I have four points to make:

First, indomethacin is a useful drug for the treatment of at least four different forms of arthritic disease. It is effective and safe as described to the medical profession.

Second, Merck answers to its own standards of research as well as to the regulatory judgment of this country and other countries throughout the world. Our standards are based upon several decades of notable accomplishments in medical research, and we give ground to no one as to the integrity of our standards and performance.

Third, the validation of the merits of our work since our studies began in 1961 up to the present can be found in the collective judgment of several hundred investigators of recognized authority in this country and abroad.

Fourth, there does not exist in this world today a generally accepted test design for the study of drugs or of any other type of therapy in rheumatoid arthritis. If there were, we would be the first to use it.

Mr. Chairman, I shall explain what we do in the study of drugs in rheumatoid arthritis. In addition, I want to point out what neither we nor others can do to study drugs in this field and why the studies conducted on indomethacin fully warrant its right to be available for physicians who wish to prescribe it for their patients.

The study of indomethacin in man dates back to 1961. At that time the cooperating clinics project of the American Rheumatism Association was still in the primitive stages of its long effort to improve clinical design in this field. We faced the task of studying a new drug shown in animal testing to possess anti-inflammatory activity comparable to steroids. The patients could not wait, nor would we wait for the design of a wholly satisfactory double-blind study for rheumatoid arthritis.

We performed what was the best method of study in 1961, and what still remains the best method in 1968. We took the drug to a handful of expert physicians in rheumatology. They began with very low doses, gradually increasing them. Under careful observation they determined the patients' positive or negative reactions. When these men told us the drug worked—that it provided relief of pain and reduction in inflammation—we accepted their judgment, both because of their knowledge and experience and also because it provided significant confirmation of the laboratory and animal work that had preceded it. After that we put the drug in the hands of additional specialists having particular expertise in a variety of arthritic disorders—rheumatoid arthritis, spondylitis, gout, osteoarthritis, musculoskeletal disorders, and so forth. As experience with the drug accumulated, we obtained the co-operation of investigators in more than 60 major medical centers in the United States and abroad. If the committee wishes, I will provide a list of these institutions for the record.

Senator NELSON. If you would, please.  
(The document referred to follows:)

**LIST OF INTERNATIONAL INSTITUTIONS WITH WHICH INDOCIN® INVESTIGATORS  
(ORIGINAL NDA) ARE ASSOCIATED**

Buenos Aires Hospital, Argentina	Sahlgren Hospital, Gutenberg, Germany.
Institute of Rheumatology, Argentina	St. Erik's Hospital, Sweden.
Karolinska Institute, Stockholm, Sweden	St. Stephen's Hospital, London, England.
Marion General Hospital, Manila, Philippines	Tokyo University Hospital, Tokyo, Japan..
Medical Institute of Rheumatology, Bogota, Columbia	Tokyo Women's Medical College, Tokyo, Japan.
Military Central Hospital, Lima, Peru	University of Florence, Florence, Italy.
National School of Medicine, Mexico	University of Frankfurt, Frankfurt, Germany.
Norfolk and Norwich Hospital, England	University Hospital of Cork, Cork, Ireland.
Osaka University Hospital, Japan	University Hospital of Wurzburg, Germany.
Oslo University Hospital, Norway	University of Paris, Faculty of Medicine, Paris, France.
Okayama University Hospital Japan	University of Vienna, Austria.
Queen Elizabeth Hospital, Adelaide, Australia	Westminster Hospital, London, England.
Royal North Shore Hospital, Australia	Kyushu University, Japan.
Royal Perth Hospital, England	
Royal Prince Alfred Hospital, Australia	
Royal Victoria Infirmary, England.	
Rheumatology Foundation Hospital, Finland.	

**LIST OF DOMESTIC UNIVERSITIES AND HOSPITALS WITH WHICH INDOCIN® INVESTIGATORS ARE ASSOCIATED**

Arkansas University Medical Center.	Tulane University School of Medicine.
Boston University Medical School.	UCLA School of Medicine.
Buffalo University School of Medicine.	UCLA Medical Center.
Children's Hospital (University of Iowa).	University of California Medical Center.
Colorado University Medical Center.	University of Chicago School of Medicine.
Columbia University College of Physicians & Surgeons.	University of Miami Medical School.
Cornell University School of Medicine.	University of Michigan School of Medicine.
Duke University Medical Center.	University of Minnesota Medical School.
George Washington School of Medicine.	University of Oregon Medical School.
Harvard Medical School.	University of Pennsylvania School of Medicine.
House of the Good Samaritan (Boston).	University of Southern California Medical School.
Johns Hopkins University Medical School.	University of Tennessee College of Medicine.
Long Island College Hospital.	U.S. Naval Hospital Newport, R.I.
Maryland University School of Medicine.	Utah University Medical School.
Massachusetts General Hospital.	Vanderbilt University School of Medicine.
Methodist Hospital (Brooklyn).	Veterans' Administration Hospital, Palo Alto, California.
New York University School of Medicine.	Veterans' Administration Hospital, Philadelphia, Pa.
New York University Medical Center.	Washington University School of Medicine.
Ohio State University School of Medicine.	Western Reserve University School of Medicine.
Oklahoma University School of Medicine.	Yale University College of Medicine.
Oregon University Medical School.	
Stanford University School of Medicine.	
Texas University Southwest Medical School.	

**Dr. LAWRAZON.** At this point, several of the investigators employed a controlled-study method known technically as placebo substitution. This is a highly useful method of confirming drug action. It is a single-blind study. Here the patient is placed on various medications including placebo at different stages, but does not know when the different drugs, which are identical in appearance, are being added or removed. These studies confirmed that the therapeutic response obtained on indomethacin was due to the drug, since the symptoms rapidly returned when the patient was given the placebo medication.

In the 1961-65 period we are discussing, this method was not only sound but respected. Even though criticized earlier in these hearings, it still remains valid today. The skilled physician, deeply concerned over the patient's comfort and progress, soon learns the characteristic pattern of the fluctuations in the activity of the individual's disease. By his experience he easily recognizes an exacerbation of symptoms of the disease, and he is able to regain control with reinstitution of the effective therapy. To imply that these clinical investigators purposely choose to institute placebo at the point in the patient's disease when the patient is about to experience an exacerbation of his illness is sheer nonsense and is a reflection on the scientific integrity of the observer and also on his moral character.

**Mr. GORDON.** May I interrupt here just a moment?

**Dr. LAWRAZON.** Yes, sir.

**Mr. GORDON.** I do not like to be in a position of defending any previous witness, but it seems to me that if a writer points out a flaw in an investigative method, I do not think he is thereby imputing dishonesty, is he?

**Dr. LAWRAZON.** I do not believe this was said, Mr. Gordon. I believe the implication was that one could give a placebo or an active compound, and then at the time one expected an exacerbation to occur or a remission, a change in the cyclic character of the disease, the investigator would change medication. This is what this refers to.

**Mr. GORDON.** Yes, but it does not necessarily impute dishonesty, does it?

**Mr. GADSDEN.** Even though I am not a doctor, I think the implied criticism of the single-blind study is that it is open to this kind of variation. If this criticism is implied, then I think Dr. Lawrason's comments are appropriate.

**Dr. LAWRAZON.** I would like to refer to Dr. O'Brien's testimony, in which he said that a study of this type—namely, the single-blind placebo—was designed in such a way that the bias is in favor of the drug.

**Mr. GORDON.** That is a statistical bias, I would think. At least, that is the way I understood it.

**Dr. LAWRAZON.** He did not say "statistical."

**Mr. GORDON.** Well, we are talking about statistics. As I said, I do not want to defend anybody, but my understanding is that the bias was a statistical bias rather than a personal bias. But I do not want to read meaning into his words.

Let me ask you this: In referring to the 1961-65 period, are you implying that clinical trials using control groups were not used before 1961?

Dr. LAWRAZON. No, the double-blind study is not new. It has been used for many years. However, the difficulties involved in rheumatoid arthritis includes the subjective character of the observations to be made. It is extremely difficult to construct a valid control study under these conditions, where active therapy is usually in the background.

Mr. GORDON. Have you any idea how many years controlled trials have been in use? I am not saying double blind, necessarily, but controlled.

Dr. LAWRAZON. Are you referring to clinical controls?

Mr. GORDON. Yes, well-controlled clinical trials.

Dr. LAWRAZON. This is nothing new. I would hazard a guess of 20 years or more.

Mr. GORDON. You may be interested to know that as a result of some research, I discovered that well-controlled clinical trials were conducted in the 18th century, about 225 years ago. It is in this book by Lind "On Scurvy," that discusses a wonderful trial he did, and I am going to include it in the record at this point, with the permission of the chairman. It is a short description of this particular trial.

(The article follows:)

[From Lind's Treatise on Scurvy, edited by C. P. Stewart and D. Guthrie, University of Edinburgh Press, pp. 145-146]

#### OF THE PREVENTION OF THE SCURVY

As the salutary effects of the prescribed measures will be rendered still more certain, and universally beneficial, where proper regard is had to such a state of air, diet, and regimen, as may contribute to the general intentions of preservation or cure; I shall conclude the precepts relating to the preservation of seamen, with shewing the best means of obviating many inconveniences which attend long voyages, and of removing the several causes productive of this mischief.

The following are the experiments.

On the 20th of May 1747, I took twelve patients in the scurvy, on board the *Salisbury* at sea. Their cases were as similar as I could have them. They all in general had putrid gums, the spots and lassitude, with weakness of their knees. They lay together in one place, being a proper apartment for the sick in the fore-hold; and had one diet common to all, *viz.*, water-gruel sweetened with sugar in the morning; fresh mutton-broth often times for dinner; at other times puddings, boiled biscuit with sugar, &c.; and for supper, barley and raisins, rice and currants, sago and wine, or the like. Two of these were ordered each a quart of cyder a-day. Two others took twenty-five gutts of *elixir vitriol* three times a-day, upon an empty stomach; using a gargle strongly acidulated with it for their mouths. Two others took two spoonfuls of vinegar three times a-day, upon an empty stomach; having their gruels and their other food well acidulated with it, as also the gargle for their mouth. Two of the worst patients, with the tendons in the ham rigid, (a symptom none of the rest had), were put under a course of sea-water. Of this they drank half a pint every day, and sometimes more or less as it operated, by way of gentle physic. Two others had each two oranges and one lemon given them every day. These they eat with greediness, at different times, upon an empty stomach. They continued but six days under this course, having consumed the quantity that could be spared. The two remaining patients, took the bigness of a nutmeg three times a-day, of an electuary recommended by an hospital-surgeon, made of garlic, mustard-seed, *rad. raphan.* balsam of Peru, and gum myrrh; using for common drink, barley-water well acidulated with tamarinds; by a decoction of which, with the addition of *cremor tartar.* they were gently purged three or four times during the course.

The consequence was, that the most sudden and visible good effects were perceived from the use of the oranges and lemons; one of those who had taken them, being at the end of six days fit for duty. The spots were not indeed at that time quite off his body, nor his gums sound; but without any other medicine, than a gargarism of *elixir vitriol*, he became quite healthy before we came into Plymouth, which was on the 16th of June. The other was the best recovered of any in

his condition; and being now deemed pretty well, was appointed nurse to the rest of the sick.

**Mr. GORDON.** So I might point out to you that a well-controlled trial was conducted as far back as the 1700's.

**Mr. GADSDEN.** I think the thrust of the remarks of the witness, Mr. Chairman, deals strictly with whether, in order to have a well-controlled test, it must be a double blind.

**Senator NELSON.** Please go ahead.

**Dr. LAWRASON.** When we take a drug such as indomethacin to the clinic, we go to the expert in the relevant discipline or specialty. We bring him in as an independent but full-fledged member of the research team. He collaborates in the planning and execution of the studies. Such experts are experienced investigators whose judgment is respected. They are independent in their actions and decisions. Their research is supported with grants for studies that often yield negative as well as positive results. I stress this relationship because we rely heavily on these investigators for the acquisition of objective observations and data on the effectiveness and safety of our drugs.

The experience and authority of the physicians who studied indomethacin, and whose judgments provided the basis for the approval of the drug, is evidenced by the following facts. Two-thirds of the indomethacin investigators in this country were Board-certified in their specialty, which is an unqualified endorsement of their training and experience. Three-quarters of them had full-time appointments with a university or a teaching hospital. Over half of them were active members of the American Rheumatism Association. I can say that the major investigations were carried out by some of the most eminent members of the American Rheumatism Association.

I would like to emphasize that we also went to the best clinics and hospitals throughout the world. These institutions are under the direction of distinguished rheumatologists. They came to the same conclusion regarding the effectiveness and safety of indomethacin as did the chemical investigators in this country.

If the cumulative judgment of this body of men is taken into account, the committee and the Food and Drug Administration, and the physicians and patients using indomethacin can be assured that the value of the drug was confirmed in the clinical judgment of an outstanding group of physicians. The criticisms that have been voiced earlier in these hearings about the testing of this drug do not represent the majority of experienced medical opinion.

The clinical program was completed in the spring of 1964. We had collected a large amount of data from 150 investigators here and abroad. The massive amount of evidence supporting efficacy and safety was submitted to the FDA for evaluation. It contained well-controlled studies and met the requirements of the preclinical and clinical standards of the day. It showed indomethacin to be safe and effective for the uses claimed. The application was approved by the FDA in June of 1965, after approximately a year of review, for the four indicated conditions for which it is labeled and promoted in the United States today.

**Senator NELSON.** Those four are rheumatic arthritis —

**Dr. LAWRASON.** Rheumatoid arthritis, gout, rheumatoid spondylitis, and osteoarthritis of the hip.

Senator NELSON. Is it indicated for any other purpose?

Dr. LAWRAZON. In this country, it is not.

Senator NELSON. Do you get a different reaction in patients in another country?

Dr. LAWRAZON. In some of the other countries some additional conditions for which we believe it is effective and safe for use are allowed. The Food and Drug Administration in this country has not allowed such other indications.

Senator NELSON. Which are the others?

Dr. LAWRAZON. Osteoarthritis in general, rather than specifically of the hip, and musculoskeletal disorders, which involve numerous disorders such as bursitis.

Senator NELSON. Why does not the FDA allow you to make these claims in this country?

Dr. LAWRAZON. I believe their reason is that they feel we have not presented them with sufficient evidence of its efficacy.

Senator NELSON. Have you presented these other countries with evidence of its efficacy?

Dr. LAWRAZON. We have presented them with a great deal of evidence. There are a great many double-blind studies ongoing and completed, and we expect within a very short time to present to the FDA evidence that will be convincing to them for efficacy and safety in these two indications.

Senator NELSON. Well, now, in how many countries do you sell this drug?

Mr. GADSDEN. Perhaps I ought to answer that. I cannot be specific with reference to this drug, Mr. Chairman, but our drugs are sold in approximately 100 countries throughout the world.

Senator NELSON. Is indomethacin sold in these 100 countries?

Mr. GADSDEN. I know drugs of Merck origin are sold in 100 countries. I do not have at the moment information as to whether "Indocid," is the trademark which is used abroad, is sold in all of these countries. I would assume that it was sold in the great majority of them.

Senator NELSON. What proof did you present to these other countries that indomethacin is effective for the additional uses that you mentioned?

Dr. LAWRAZON. In the original application, there was substantial evidence of its efficacy in these other indications. Since then, we have submitted a supplement to the NDA which provided additional evidence as to its efficacy and safety. This same evidence has been presented to other regulatory agencies in other countries. When reviewed by these other agencies, they have come to the conclusion that it is safe and effective in these indications and have allowed it use.

Senator NELSON. Do each of these 100 countries have an agency of scientists who evaluate the information you supply and make a judgment?

Mr. GADSDEN. May I respond to that, sir?

Senator NELSON. Yes.

Mr. GADSDEN. The answer, as I think you might know, is that not all do have such an agency. It is the more developed countries, particularly of Western Europe that do, and even there not all of them. But I would agree with you if your point is that there are countries which do not have such regulatory control.

**Senator NELSON.** This puzzles me a little bit, not necessarily about this drug in particular, but about any drug. If the country does not have a qualified scientific agency to make a judgment, then a drug can be advertised and sold for any purpose the company desires to sell it for, can it not, regardless of whether it is indicated or not?

**Mr. GADSDEN.** I would have to agree that it could be, but I do not think a responsible company would do so, sir.

**Senator NELSON.** We had the case here of chloramphenicol being promoted in Great Britain with no precautions being given in the ads at all. At the same time, the firm testified here that it agreed that all the specific precautions in the package insert required here were important and necessary and should be listed. Yet in Great Britain and other countries, the firm said it did not list these because the law of those countries did not require them.

What I am getting at is the claims of the company that they follow a very ethical, high standard. Yet here is a clear-cut case where as soon as there are no regulations, they promote the drug for a purpose which is illegal in this country, and without any precautions, contrary to the best testimony of all the medical experts in America.

**Mr. GADSDEN.** Sir, I do not want to be put in the position of talking about whether the conduct of a competitor was appropriate or not. But if you like, I have a statement here which I would be happy to read indicating that the British Pharmaceutical Association, working with the appropriate medical and regulatory bodies in England, concluded that—in advertising—it was undesirable to put such contraindications and warnings in the advertisement when it was a so-called reminder advertisement. I think that the earlier witness who was questioned on this, if my memory is correct, was perhaps not conversant with the subject of advertising.

**Senator NELSON.** What is your definition of a reminder ad?

**Mr. GADSDEN.** In this case, sir, this is one—

**Senator NELSON.** In any case, what is, in your industry, the definition of a reminder ad?

**Mr. GADSDEN.** I shall have to give you several definitions, sir.

In the United States, the Food and Drug Administration has taken a very narrow definition of what is a reminder ad and we comply with that.

In England, with the agreement of the British medical group and the appropriate governmental authority, it was stated that if there was no dosage indication which would be helpful to the physician in prescribing the product, that is a reminder ad. The editor of the British Medical Journal said he considered it an insult to the intelligence of the British physician to include such material.

**Senator NELSON.** So, that is different from the reminder ad in America, in which you cannot include any language indicating the usage of the drug; is that correct?

**Mr. GADSDEN.** Yes.

**Senator NELSON.** But you can in England and you need not put any warnings or precautions about its use in the ad; is that correct?

**Mr. GADSDEN.** It is a broader definition in England, where the definition of a reminder ad is any advertisement in which information with reference to dosage is eliminated.

**Senator NELSON.** In this country?

Mr. GADSDEN. No, sir; I said in Great Britain.

Senator NELSON. That is not a reminder ad in this country. In other words, you usually do not put dosages in your ads anyway, do you, in this country or in any country?

Mr. GADSDEN. We frequently do, sir, in this country. I think the basic point, which is perhaps going to crop up on several occasions, is that when you are an international company and doing business in a variety of countries, quite naturally your foreign subsidiaries must conduct themselves in accordance with the local practices, laws, and regulations of that country—which, in many cases, differ from the regulations in this country as promulgated by the Food and Drug Administration.

Senator NELSON. How do you view the problem of a country that does not really have any agency for evaluating drugs at all?

Mr. GADSDEN. Well, I think we get back to the statement of one of our scientific witnesses—I trust you will permit me to speak just for Merck & Co., because I am neither authorized nor competent to speak for anyone else—that we have our own internal code of ethics with reference to what is appropriate. When, in the opinion of our medical research group, it is concluded that a statement is appropriate to make in these countries, the medical research people have the authority to make the decision that it can and should be made.

Senator NELSON. What bothers me about that is that even in this country, there are disputes among the industry and doctors and the FDA about the promotion of drugs. The argument on the part of those who think drugs are overprescribed is that it is the result of this type of advertising and promotion, despite the insistence of the FDA that package inserts contain certain warnings and contraindications and so forth. The consequence of the advertising, in any event, is that many drugs are widely overprescribed for nonindicated cases. At least, the testimony we have had on some drugs from experts is that this is the fact.

So the result of the advertising and the promotion, even with FDA monitoring what is said in the package insert and in the advertising, is overprescription of many drugs for nonindicated uses. If that is the case in this country where you have a regulatory agency, it certainly must be the case in those countries where you do not have one. It seems to me that there should be in that instance, very important internal restraints upon a company advertising in such a country.

Mr. GADSDEN. I would agree with you, sir. But if you have a code of morals and ethics, you must adhere to it and not take advantage of the fact that you may not get caught somewhere.

Senator NELSON. But let me proceed with this. If you have an underdeveloped country, or any country without a sophisticated scientific community and without a regulatory agency so that it cannot protect itself, what is your standard of guidance for advertising in that country?

Mr. GADSDEN. Our standard of guidance, sir, is whatever has been approved by the scientists of Merck as the appropriate medical positioning of the product.

Senator NELSON. Then you do not use the standard of what is approved by FDA in this country?

Mr. GADSDEN. No, we do not.

Senator NELSON. So you feel that your company, or any company, ought to be able to decide on its own what the standard will be in a country which has no scientific community or regulatory agency at all?

Mr. GADSDEN. No, sir, I do not think I have said that.

Senator NELSON. That is exactly what you said, that you decide what the standard is.

Mr. GADSDEN. I beg your pardon, sir?

Senator NELSON. Please repeat what you have said.

Mr. GADSDEN. I said that in this matter, Merck & Co.—and I refer to my earlier statement that I speak only for Merck & Co.—we have a code of ethics and principles. We assume responsibility for the positioning of the product. This reference to this was made in Dr. Lawrason's statement, I believe. We hold our medical staff responsible. They must approve what is said, whether it be in the United States or any country of the world. This, for Merck, is the restraint under which we operate.

Senator NELSON. I did not get the distinction between what you said and what I said. I said you set the standard.

Mr. GADSDEN. Sir, may I paraphrase what I understood you to say? I think you said, if I understand you correctly, that it is appropriate for Merck or any other company, in countries where there are no regulating agencies, to say what it wants in advertising.

Senator NELSON. To set your own standard, I think I said.

Mr. GADSDEN. I am sorry, perhaps I misunderstood you.

Senator NELSON. That is what I intended to say. In other words, you are saying that in another country where there is no scientific community to evaluate the evidence you have, a company sets its own standards without any outside control. Is that what you have said?

Dr. LAWRAZON. Mr. Chairman, may I just say that we do not set separate standards for different countries. We have a single standard at Merck.

Senator NELSON. You mean you run precisely the same ad in the Philippines that you run in the British Medical Journal?

Dr. LAWRAZON. No, I am referring to how the drug can be used and what indications are to be cited—in other words, the claims made for the drug and which diseases it should be used for.

Senator NELSON. I do not quite follow that. The FDA will not permit you to use it in this country for—what were the indications?

Dr. LAWRAZON. Osteoarthritis.

Senator NELSON. And that involves tendonitis?

Dr. LAWRAZON. No, sir; that was the musculoskeletal.

Senator NELSON. And that involves tendonitis and bursitis. The FDA says you cannot use it because you have not submitted, as far as they are concerned, satisfactory evidence or proof of its efficacy, for those conditions.

Dr. LAWRAZON. That is correct.

Senator NELSON. Now you go to England and you advertise it for that purpose, and the British will say that it is all right for that purpose. Then, you may go to another country and they will say it is all right for all the purposes you use it for in America plus one other, but not two. Then you go to another country, that has no scientific community, and you claim that it is good for some other purposes and you advertise it and sell it for those purposes in that country if your

scientists and you come to the conclusion that it is useful for those purposes, would you not?

Mr. GADSDEN. Perhaps I should explain to you, sir, what is the procedure. In the internal workings of Merck & Co., a scientific and medical evaluation is made which ultimately results in an application for new drug approval. The thing I want firmly on the record, in case there is any question about it, is that we do not sell abroad—I think I am right—anything for which approval has not been requested of the Food and Drug Administration in the United States.

Senator NELSON. I do not understand.

Mr. GADSDEN. Well . . . if we are not willing to report it to the Food and Drug Administration, we are not going to say in an underdeveloped country that it will cure something for which we are not requesting approval in the United States.

Senator NELSON. I understand. But if you request approval in the United States for its use for a certain purpose and the FDA says that so far as they are concerned, your scientific submission of evidence does not support its use for that purpose, and they turn you down, you still will sell it for that purpose in an underdeveloped country that has no scientific community at all?

Mr. GADSDEN. Yes, sir; we will.

Senator NELSON. I am not saying that some company may not make a mistake; it may turn out to be right and the FDA wrong. The principle that bothers me is there are lots of companies in this business that may not be as conscientious as Merck, and you will end up with all the companies supplying drugs to other countries that do not have drug standards, so that a drug might be used for purposes that it should not be. We have had testimony here that drugs which could not be sold in this country because they did not meet U.S.P. standards were shipped overseas—not your company. I am just raising the question, because it seems to me that if that testimony was correct on subpotent drugs which could not go on the market here being sold in South America, I think it ought to be explored from the standpoint of some legislation. I do not think anybody ought to have a license to put drugs on any market that do not meet a reasonable standard in this country.

Mr. GADSDEN. I agree with you, but I think you yourself said earlier that there are differences in medical opinion, and this can result in the Food and Drug Administration's concluding in all sincerity that they do not think the evidence complies with the law and regulations under which they operate, and yet in the opinion of the American scientists it is believed that there is substantial evidence.

Senator NELSON. That is bound to be the case: there is no question about that.

While I am on that point, it is agreed, as I understand it, that indomethacin is not indicated for use in children?

Dr. LAWRAZON. Indomethacin?

Senator NELSON. That is right. It is not indicated for use in children; is that correct?

Dr. LAWRAZON. It is contraindicated in this country at the request of the Food and Drug Administration.

Senator NELSON. Is it indicated in other countries for use in children?

Dr. LAWRAZON. There are other countries that feel the indications for the efficacy and safety of the drug warrants its being used in children; that is correct.

Senator NELSON. I think it is an interesting point just to put into the record at this stage on the question of uses of the drug in this country that in a study done by Modern Medicine of August 1, 1966—I will submit it for the record so I do not have to go through it all—it was found that within 1 year after it went on the market indomethacin was used in pediatrics by 9.4 percent, I believe, of pediatricians who answered questionnaires; 9.4 percent of the pediatricians were using indomethacin despite the fact that the FDA has not approved it for pediatric use in this country.

Mr. CUTLER. Could you give us the date, Senator Nelson?

Senator NELSON. Yes, the results of the poll appear in the August 1, 1966, issue of Modern Medicine.

Mr. CUTLER. What was the date of the poll, sir? Does that show?

Senator NELSON. Well, let me see. It was published August 1, 1966. It may be in here, but I do not see the date of the poll.

(The document referred to follows:)



# Poll on Medical Practice

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## RHEUMATOID ARTHRITIS

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How do physicians treat rheumatoid arthritis today? Are there notable differences from region to region? Between internists and physiatrists? Between large cities and small towns? Some of the answers are on the following pages.

This report contains the most important portions of the analyses carried out on the basis of a questionnaire sent to all *Modern Medicine* readers. No attempt at this time is made to present or detail all of the analyses, or to comment on the significance of these analyses. It is the purpose of this report to present the findings without expression of either approval or disapproval.

The fact that nearly 12,000 physicians took time from their busy lives to answer this questionnaire on rheumatoid arthritis demonstrates a high degree of interest and provides considerable validity to the answers obtained in the questionnaire. Continued reader cooperation with future questionnaires will provide readers and editors with an interesting and revealing series of shared experiences.

IRVING S. WRIGHT, M.D.  
*Editorial Consultant*

WYMAN E. JACOBSON, M.D.  
*Associate Editor*

## 11,603 Respond to Questionnaire

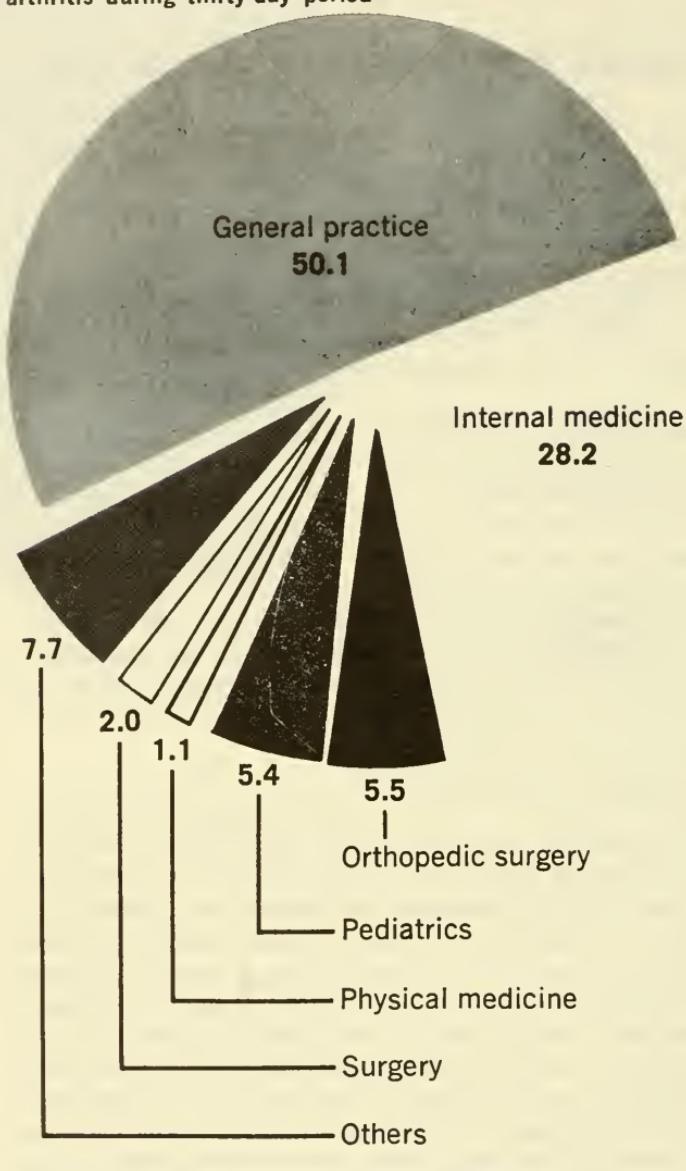
Of the 11,603 physicians who responded to the questionnaire, 5,694 (49.1%) reported that they had treated patients with rheumatoid arthritis within a period of thirty days. Of those reporting treatment, 50.1% were general practitioners, 28.2% internists, 5.5% orthopedic surgeons, 5.4% pediatricians, 2% surgeons, 1.1% physiatrists, and 7.7% other specialists (Fig. 1). Nearly eight out of ten physicians who treated patients with rheumatoid arthritis were either general practitioners or internists.

An "open-end" questionnaire was employed to eliminate or reduce to a minimum the factors which might cause an intrinsic bias or result in responses based on the "correct answer" rather than on the true practice of the physician. Accuracy of the responses was considered best achieved by short recall—thirty days—which in most instances would not require review of patients' charts or lead to unreliable guesses. One-half of the physicians reporting therapy treated no more than one new case and no more than four follow-up cases of rheumatoid arthritis in a thirty-day recall period.

### Analysis of treatment

Table 1 represents the analysis of treatments employed and of patients treated for rheumatoid arthritis during the thirty-day period. The 5,694 physicians used an average of 2.72 methods of treatment and treated a total of 104,010 patients. Major categories of methods used were systemic drug treatment, nondrug treatment, and external drug treatment; in a small sample, method of treatment was unknown or not clearly indicated. The categories of systemic drugs included [1] analgesics and combinations, [2] adrenal steroid hormones and combinations, [3] gold, [4] nonsteroid anti-inflammatory drugs, and [5] a group of miscellaneous drugs, none of which was utilized to any large extent even when the agents were combined in subgroups on the basis of chemical or pharmacological characteristics.

Fig. 1. Type of practice of physicians who treated rheumatoid arthritis during thirty-day period



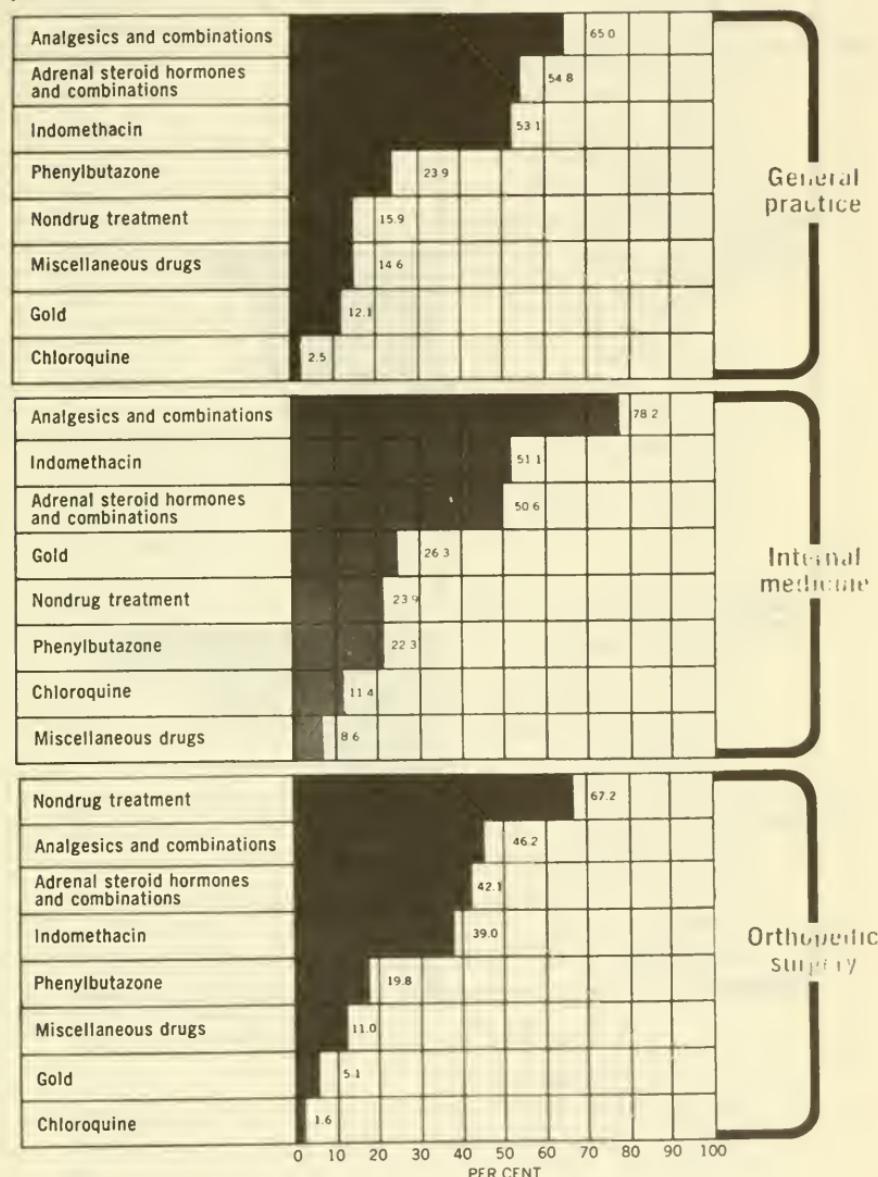
**Poll / RHEUMATOID ARTHRITIS****Table 1. Methods of treatment used for rheumatoid arthritis**

<b>Category</b>	<b>Percent of treatments mentioned</b>	<b>Percent of patients mentioned</b>	<b>Number of patients mentioned per treatment mentioned</b>
<b>Systemic drug treatment</b>	<b>87.1%</b>	<b>79.6%</b>	<b>6.13</b>
Analgesics and combinations.....	25.9%	28.4%	7.37
Aspirin, salicylates, and salicylate compounds	24.1	26.8	7.43
Other or unspecified	1.8	1.6	6.43
Adrenal steroid hormones and combinations.....	22.2%	16.2%	4.87
Cortisone and combinations	1.8	1.4	5.15
Prednisone and combinations	5.4	3.1	3.82
Prednisolone and combinations	1.9	1.4	4.73
Methylprednisolone and combinations	1.5	1.0	4.36
Triamcinolone and combinations	1.6	1.0	4.35
Dexamethasone and combinations	1.7	1.1	4.46
Hydrocortisone and combinations	0.5	0.3	4.55
Other corticosteroids or unspecified and combinations	6.6	5.9	6.03
Adrenocorticotropic hormone	1.2	1.0	5.13
Gold .....	5.5%	4.8%	5.90
Nonsteroid anti-inflammatory drugs.....	27.4%	22.1%	5.41
Indomethacin	17.3	14.3	5.56
Phenylbutazone	8.2	5.8	4.74
Chloroquine	1.9	2.0	6.97
Miscellaneous drugs .....	6.1%	8.1%	8.96
Muscle relaxants	0.6	0.7	8.53
Tranquilizers and sedatives	0.6	0.7	8.68
Vitamins	1.3	2.0	10.39
Narcotics and combinations	0.3	0.3	8.14
Anabolic agents	0.1	0.2	9.71
Vaccines	0.3	0.5	10.20

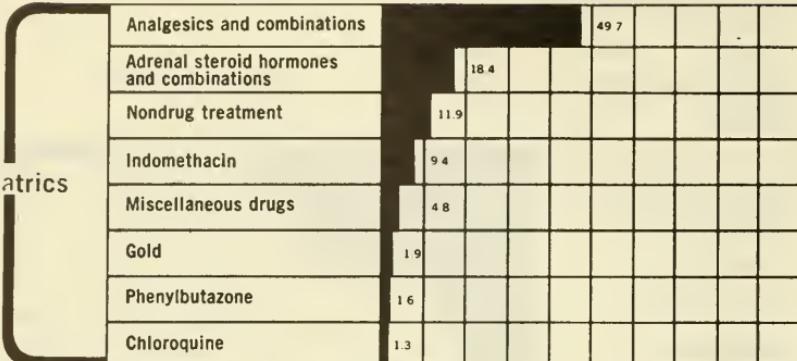
Category	Percent of treatments mentioned	Percent of patients mentioned	Number of patients mentioned per treatment mentioned
<b>Systemic drug treatment (cont.)</b>			
Antibiotics and chemotherapeutics	0.5	0.5	6.15
Colchicine and combinations	0.2	0.3	9.19
Probenecid and combinations	0.1	0.1	5.35
Nonadrenal hormones	0.3	0.4	9.56
Others	1.8	2.4	9.10
<b>Nondrug treatment</b>	<b>11.5%</b>	<b>19.4%</b>	<b>11.33</b>
Physical therapy .....	9.6%	16.9%	11.84
Heat	2.3	3.4	10.11
Rest	1.9	3.2	11.38
Exercise	1.3	2.3	11.62
Other or unspecified	3.8	7.4	13.05
Osteopathic manipulation	0.3	0.6	13.58
Surgery .....	1.0%	0.8%	5.46
Miscellaneous nondrug treatment.....	0.9%	1.7%	12.50
X-ray	0.1	0.0	4.56
Diet	0.6	1.4	14.21
Psychotherapy	0.2	0.3	10.69
Other or unspecified	0.0	0.0	3.17
<b>External drug treatment</b>	<b>0.2%</b>	<b>0.2%</b>	<b>6.42</b>
<b>Therapy unknown or unclear</b>	<b>1.2%</b>	<b>0.8%</b>	<b>4.60</b>
Base	100.0%	100.0%	6.71
	(15,494)	(104,010)	

**Poll / RHEUMATOID ARTHRITIS**

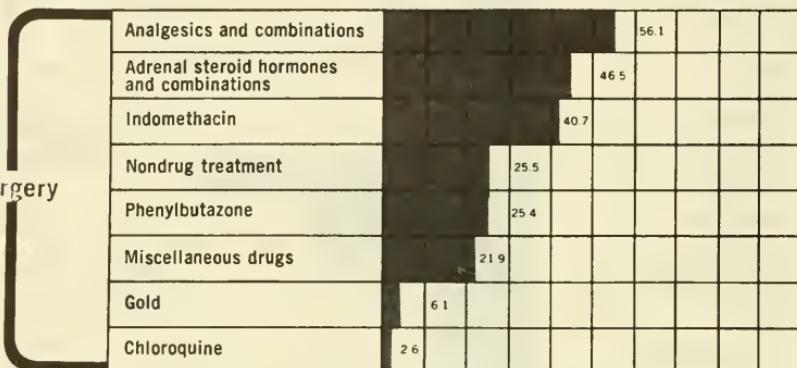
**Fig. 2. Treatment of rheumatoid arthritis according to type of practice**



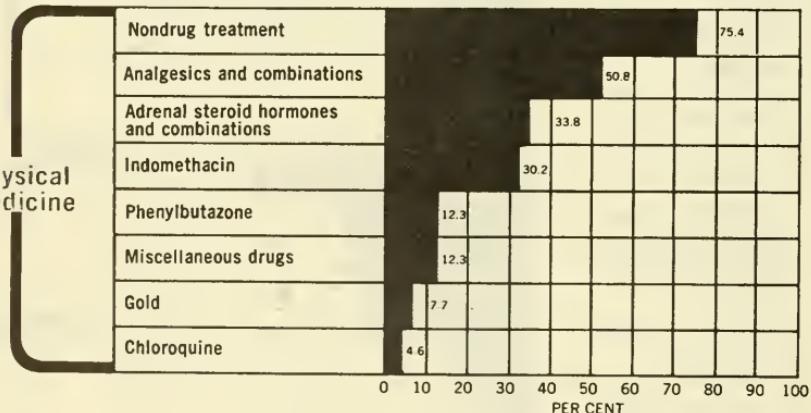
## Pediatrics



## Surgery



## Physical medicine



**POLL / RHEUMATOID ARTHRITIS**

Although the nonsteroid anti-inflammatory drugs were prescribed more often than the other systemic agents, the three drugs included in this category—indomethacin, phenylbutazone, and chloroquine—are different enough to warrant individual consideration. The analgesics and combinations (primarily salicylates) accounted for more than one-quarter of all the treatments, the adrenal steroid hormones and combinations for slightly less than one-quarter, and indomethacin for approximately one-sixth. In the nondrug treatment category, physical therapy was prescribed most often and accounted for about one-tenth of all the treatments.

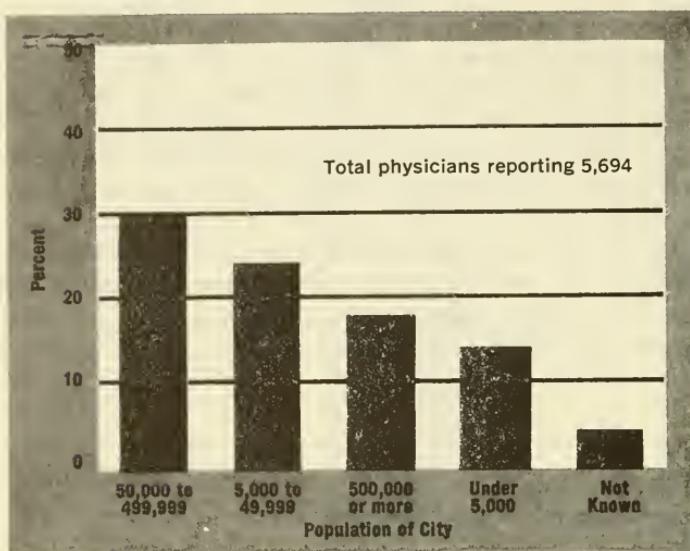
The data on treatment were also processed in relation to the 104,010 patients receiving therapy. Some major differences were noted when the percent of patients mentioned was compared with the percent of treatments mentioned. Although the adrenal steroids were reported in almost one-quarter of the responses, these drugs were used in only one-sixth of the patients. The nonsteroid anti-inflammatory drugs were reported in 27% of the returns but used in only 22% of the patients, salicylates in one-fourth of the returns but in more than one-fourth of the patients, physical therapy in one-tenth of the reports and one-sixth of the patients, and total nondrug therapy in one-tenth of the returns but one-fifth of the patients.

In the data processing, medications combining two or more of the major systemic drugs were included in the group in which the drug was considered to have the strongest pharmacological action in the opinion of the medical editor. Thus, combinations of aspirin and adrenal steroids were included with the adrenal steroid hormones, since the predominant pharmacological action was considered to be due to the hormone.

**Methods of treatment by type of practice**

General practitioners and internists utilized analgesics, adrenal steroids, gold, and indomethacin to a greater extent than did the other specialists (Fig. 2). Among the 2,852 general practitioners who reported

Fig. 3. Distribution of physicians by city size who treat rheumatoid arthritis



treatment of rheumatoid arthritis during the thirty-day period, 65% prescribed analgesics and combinations, 54.8% adrenal steroid hormones and combinations, 53.1% indomethacin, 23.9% phenylbutazone, and less than 20% any of the other single categories.

Among the 1,606 internists, 8 out of 10 prescribed analgesics and combinations, 5 out of 10 indomethacin or adrenal steroid hormones, 2.5 out of 10 gold, and 2 out of 10 phenylbutazone or physical therapy. This is in sharp contrast to the 310 pediatricians, who relied primarily on analgesics and combinations (5 out of 10) but only infrequently prescribed indomethacin, phenylbutazone, or gold. It is of considerable interest that the surgeons, orthopedic surgeons, and physiatrists used adrenal steroids and indomethacin frequently (3 to 5 out of 10 physicians) but rarely used gold. The internists used gold therapy much more often than did any of the other specialists.

This analysis reveals major differences in treatment based on the type of practice, some of which are directly related to the nature of the specialty; explanations of other variations are less obvious.

Poll / RHEUMATOID ARTHRITIS

### Variations in treatment based on other factors

The data were evaluated in relation to age of the physician, size of the locality in which the physician practiced, and the geographic location on a national basis. Of the 5,694 physicians who reported treatment of patients with rheumatoid arthritis, one-fifth were in cities of 500,000 or more population and one-sixth in communities of under 5,000 (Fig. 3).

Physicians in smaller cities and towns prescribed indomethacin more frequently than did physicians in larger cities: 55% of physicians in areas of under 5,000 persons, but only 38% of those in cities of 500,000 people or more, prescribed indomethacin. On the other hand, physical therapy and surgery were employed more frequently in the larger cities than in communities of under 5,000 population.

The methods of treatment varied with the age of the physician, but only a couple features were rather prominent. Physicians age 65 years or older used gold only about half as frequently as did those age 64 or younger. Physicians 35 to 64 years of age used gold therapy with about the same frequency. Physicians under 35 years of age used adrenal steroid hormones less frequently than did the middle-aged and older physicians. However, the younger physicians used indomethacin and surgery considerably more often than did the physicians age 65 or over.

### Results of treatment

Obviously, the most difficult evaluation is that related to the results of treatment. The questionnaire made no attempt to provide any more than a crude estimate by the attending physicians as to the nature of the response. Physicians were asked to estimate the percentage of patients who apparently recovered, showed improvement, and showed no improvement and in whom the condition was arrested. The results of this evaluation are shown in Table 2. Approximately two-thirds of the patients who were treated either showed improvement or apparently recovered.

**Table 2. Results of treatment of rheumatoid arthritis (estimated percentage of cases)**

	Mean average percent
Apparent recovery	5
Improvement shown	60
Condition arrested	19
No improvement shown	16
<b>Total (Base: 4,477)</b>	<b>100</b>

**Major changes in treatment from 1949 to 1966**

In 1949, *Modern Medicine* attempted to evaluate the treatment of rheumatoid arthritis. Results of that survey were compared with those of the 1966 study (Table 3), though the two surveys were not comparable in question form. The 1949 questionnaire listed five specific types of treatment: drugs, vaccines, diet, physiotherapy, and orthopedic procedures. The obvious differences are in relation to medications which were not available in 1949—namely, the adrenal steroid hormones and the nonsteroid anti-inflammatory drugs. The analgesics and combinations accounted for approximately one-third of the treatments in both studies. Gold was used almost twice as frequently in 1949 as in 1966. The large miscellaneous group in 1949 included drugs only. Vaccine was used in 27% of the prescriptions in 1949 but in only 0.9% in 1966.

**Table 3. Comparison of drugs prescribed in 1949 and 1966**

	1949 Percent	1966 Percent
Analgesics and combinations	32.7	29.7
Adrenal steroid hormones and combinations	—	25.6
Gold	11.5	6.3
Nonsteroid anti-inflammatory drugs	—	31.4
Miscellaneous	55.8	7.0
<b>Total</b>	<b>100.0</b>	<b>100.0</b>

**Poll / RHEUMATOID ARTHRITIS**

**Fig. 4. New cases and follow-up cases of rheumatoid arthritis treated during a thirty-day period**

New cases treated											
	Mean	1	2	3	4	5	6	7	8	9	10
All physicians	2.55	○	○	○							
Physiatrists	4.44	○	○	○	○	○					
Orthopedic surgeons	3.40	○	○	○	○	○					
Internists	2.61	○	○	○							
General practitioners	2.59	○	○	○							
Surgeons	2.51	○	○	○							

Follow-up cases treated											
	Mean	1	2	3	4	5	6	7	8	9	10
All physicians	7.47	○	○	○	○	○	○	○	○	○	
Physiatrists	9.78	○	○	○	○	○	○	○	○	○	○
Internists	9.11	○	○	○	○	○	○	○	○	○	○
Orthopedic surgeons	8.03	○	○	○	○	○	○	○	○		
General practitioners	7.47	○	○	○	○	○	○	○	○		
Surgeons	5.79	○	○	○	○	○	○				

### The physician and rheumatoid arthritis patient population

The physiatrists had the largest mean average (4.44) of new cases during the thirty-day period. The orthopedic surgeons reported a mean average of 3.40 new cases, the internists 2.61, the general practitioners 2.59, and the surgeons 2.51 (Fig. 4). Although the *mean* average of new cases for all physicians was 2.55, the *median* average was 1.00, i.e., 50% of the physicians had more than one new patient and 50% had less than one.

The physiatrists also had the largest mean average (9.78) of follow-up cases of rheumatoid arthritis during the thirty-day period. The internists had a mean average of 9.11 such cases, the orthopedic surgeons 8.03, the general practitioners 7.47, and the surgeons 5.79 (Fig. 4). Although the *mean* average of follow-up cases for all physicians was 7.47, the *median* average was 4.00, i.e., 50% had more than four follow-up cases and 50% had less than four.

### The questionnaire and its validity

The questionnaire on rheumatoid arthritis (Fig. 5) was included in all copies of the March 14, 1966, issue of *Modern Medicine*. Four weeks after release

Fig. 5. Doctors were asked these questions:

1. Do you attend patients with rheumatoid arthritis?  
Yes \_\_\_\_\_ No \_\_\_\_\_
2. How many patients have you seen for the first time with rheumatoid arthritis during the past 30 days? \_\_\_\_\_  
(number)
3. How many patients have you seen on subsequent visits for rheumatoid arthritis during the past 30 days? \_\_\_\_\_  
(number)
4. How did you treat the patients you saw during the past 30 days?
5. What results have you experienced over the past year with your treatment of rheumatoid arthritis? (Estimate by percentage of cases.)

**Poll / RHEUMATOID ARTHRITIS****Table 4.** Type of practice of physicians replying to questionnaire compared with that of total U.S. physician population

Type of practice	Physicians replying to questionnaire		Total U.S. physicians
	Number	Percent	Percent
General practice	3,200	27.6	34.4
Internal medicine	1,784	15.4	12.9
Surgery	1,005	8.7	9.6
Obstetrics and gynecology	776	6.7	6.9
Pediatrics	710	6.1	5.7
Eye, ear, nose, and throat	639	5.5	5.8
Psychiatry	484	4.2	5.0
Orthopedic surgery	380	3.3	2.9
Radiology	372	3.2	3.2
Anesthesiology	340	2.9	3.4
Dermatology	299	2.6	1.5
Urology	193	1.7	2.0
Pathology	192	1.4	1.4
Neurology	170	1.5	1.3
Allergy	126	1.1	0.4
Cardiovascular disease	111	1.0	0.6
Physical medicine	70	0.6	0.2
Thoracic surgery	66	0.6	0.6
Preventive medicine	58	0.5	0.3
Plastic surgery	53	0.5	0.5
Colon and rectal surgery	52	0.4	0.3
Gastroenterology	40	0.3	0.2
Pulmonary disease	21	0.2	0.2
Other	462	4.0	0.7
<b>Total</b>	<b>11,603</b>	<b>100.0</b>	<b>100.0</b>

of the questionnaire, more than 11,800 responses had been received. Of these, 11,603 were satisfactory for data processing and tabulation: 3,200 from general practitioners, 1,784 from internists, 1,005 from surgeons, 710 from pediatricians, 380 from orthopedic surgeons, 70 from physiatrists, and 4,454 from physicians of other specialties (Table 4).

Almost all responders, classified according to their specialty or primary type of practice, are represented in about the same proportion in the survey as in the national distribution of the physician population (Table 4). Among the general practitioners, 89.1% reported treating patients with rheumatoid arthritis, among the internists 90%, among the physiatrists 90%, and among the orthopedic surgeons 82.9%.

**Table 5. Regional distribution of physicians replying to questionnaire and of all physicians in the United States**

Region	Physicians replying to questionnaire		All physicians in U.S.* Percent
	Number	Percent	
New England	722	6.2	6.6
Mid-East	2,291	19.7	23.0
South Atlantic	1,413	12.2	12.7
Great Lakes	1,816	15.7	18.0
Mid-South	481	4.1	4.8
Plains	955	8.2	7.2
Southwest	856	7.4	7.9
Rocky Mountain	549	4.7	3.8
Far West	1,793	15.5	15.5
Pacific	55	0.5	0.5
Unknown	672	5.8	—
<b>Total</b>	<b>11,603</b>	<b>100.0</b>	<b>100.0</b>

\*Source: Buckley Dement

**Poll / RHEUMATOID ARTHRITIS**

The large size of the response, the representative distribution by all types of practice, and the geographic distribution of the responders are considered evidence for reliability of the data in this report. With only minor variations, the return on this poll was highly comparable to the distribution of all physicians by states and regions. Table 5 shows this comparison for regions only, but the analysis by the editors included comparison for all fifty states.

Questionnaires are often considered somewhat suspect. It is therefore important that the objectives of the questionnaire which we have presented for your help and ultimate information be restated. The diagnostic and therapeutic measures used by physicians are known to vary considerably. The factors associated with these differences are not known. Teachers in medical schools do not know whether their instructions and recommended forms of treatment have been adopted by their students. Those planning postgraduate training courses do not know what their prospective matriculates have been using in their own practices. Neither the American Medical Association nor the Department of Health, Education, and Welfare can provide detailed information on the actual practices—and the practitioner does not know what his confreres are doing. The purpose of this project is to answer some questions regarding certain leading causes of death and disability. The editors will compile the information which you provide as the practitioners representing different types of practice, all age groups, and wide geographic distribution.

The aim is to determine what is going on. *These findings are not to be considered as endorsement or condemnation of any form of treatment.* The editors of this section will operate with complete independence and detachment in this regard. If others see fit to use this material to strengthen their teaching programs, to read further information into the various forms of treatment which appear to be widely used, or to vent their opinions in the literature regarding these findings, this series will have served some useful purpose.

Senator NELSON. The point I was making is we continue to have cases arise of drugs being used for conditions in which they are not indicated. The dramatic one was brought out in the testimony of several distinguished doctors, including Dr. William Damashek of Mount Sinai Hospital, that chloramphenicol was being used at least 90 percent of the time in nonindicated cases. So, despite the warnings in the package insert, the promotion of the drug or some other factor was causing doctors to prescribe it widely, as the testimony showed, for head colds, minor infections, acne, hangnails, and toe infections. We have cases by the dozens in my files, and testimony of deaths caused by Chloromycetin. All of them resulted from the drug having been given when it was not indicated. All I am pointing out is that we continue to get this kind of evidence. This committee is interested in the question of drug promotion and promotion resulting in the use of drugs in cases which are nonindicated.

The questionnaire I referred to was sent on March 14, 1966.

Mr. GADSDEN. Sir, I think you will appreciate that we are at some disadvantage in trying to comment on this because we do not have it. If you will permit me, I would not like the record to show this juxtaposition between indomethacin and chloramphenicol. I am not qualified to talk about chloramphenicol. I am prepared to talk about indomethacin.

Senator NELSON. I did not use that example to compare them at all. I was just saying that pediatric use of Indocin is not indicated in this country, and in this poll, 9.4 percent of the pediatricians who responded, were using it on occasion for this purpose. I am only pointing out that we hear evidence time after time about drugs that are being used for nonindicated purposes.

I think that part of the cause for such misuse is the dramatic and effective promotion of the drug.

Mr. GADSDEN. Well, sir, as you know, I will be the last witness. I am sure you will have some questions for me on what we have done in the way of promotion for "Indocin."

Senator NELSON. Senator Hatfield has a question.

Senator HATFIELD. Doctor, there are a couple or three questions that come to mind at this point: First of all, as I understand your testimony, you indicated that you submit to the FDA a great mass of material, pretests, research when you are submitting a new drug for approval. Do you feel that the FDA is presently equipped, both with manpower and staff generally, to handle this type of responsibility adequately?

Dr. LAWRAZON. I believe that it is generally recognized that this is a terribly difficult job—evaluation of drugs, review of all the information, the data that is submitted on each new application. My opinion is that they need every support and every bit of help, scientific and medical help, they can get to review these applications.

Senator HATFIELD. Now, this mass of material that you submit—I understand, for example, that they have what, a staff of 170 to review 2,000 or more applications? Can they adequately and effectively read and review all of this mass of material that you and each other drug house submits for this New Drug Application?

Dr. LAWRAZON. I believe the past 2 or 3 years have been rather difficult times for the agency because they have had a backlog which

they, I believe, have effectively reduced or are effectively reducing. I am not quite sure that the 2,000 you are quoting is an ongoing total amount that is constantly before them.

Senator HATFIELD. I think the figure is about 2,600, the latest figure that I obtained on that. Do you think it is possible in terms—

Senator NELSON. May I interrupt you? I think the record ought to show, Senator, that the 2,600 represents active IND's.

Senator HATFIELD. These are applications.

Senator NELSON. These are active IND's, I believe.

Mr. GADSDEN. I do not have that figure. Just to amplify Dr. Lawrason's remarks, Merck and the industry have, over the years, supported the FDA in their applications for additional funds and additional people, because we are appreciative of the problems which they have in trying to deal with very complex subject matter.

Senator NELSON. Testimony on this subject is in the record as of yesterday or the day before.

Senator HATFIELD. I would like to be sure that we have the exact figure in relation to whether it is NDA or IND at this place in the record.

Do you think there could be a better system devised, such as perhaps utilizing outside consultants, or do you think it should just be a bigger bureaucracy? Of course, you realize I do not have much faith in the bureaucracy that exists there now. But are you indicating to me that we should just add more and more staff to an already rather inefficient operation?

Dr. LAWRAZON. Senator, I would hate to make suggestions on how to solve some of these problems of the Food and Drug Administration.

Senator HATFIELD. Would you like to comment on the bill that I have introduced to take all this away from the FDA and put it in the competent hands of the National Academy of Sciences?

Dr. LAWRAZON. I would not want to.

Senator HATFIELD. You would not care to?

Dr. LAWRAZON. No.

Senator HATFIELD. I understand why perhaps you might not want to at this point.

What would you say as to the second problem that bothers me? That is that you indicate, like your other colleagues in the industry, that you accumulate a mass of material to have the FDA review and study for these approvals, but what kind of continuing research do you have? What kind of continuing program is there to review the effects after a longtime use of these drugs? I have at no point found any satisfactory evidence that there is such a continuing research by industry or of review by Government on the effects that might occur after—not the initial efficacy or the purpose for which it was originally taken, but the side effects or other things that can happen after long term use of the drug?

Dr. LAWRAZON. Senator, I can give you some figures on the extent of our continuing investigation of indomethacin which I think will be pertinent to these hearings. As you will recall, seven controlled studies, not all double-blind, were submitted with the New Drug Application.

Since then, four additional double-blinds have been completed. There are now nine others ongoing in rheumatoid arthritis, with an additional four to six with other controls, other drugs. The total,

including these double-blind studies, is 131 studies now ongoing in the various indications.

We have 26 in rheumatoid arthritis, 21 in osteoarthritis, two in osteoarthritis of the hip, 22 in musculoskeletal disorders, and 60 others which involve the investigation of the drug as an analgesic and anti-pyretic for thrombophlebitis and so forth.

Senator HATFIELD. What is the span of time in which these are continuing? What is your general control period?

Dr. LAWRAZON. The general control period extends, for each study, anywhere from 2 weeks to 3 months.

Senator HATFIELD. But what about beyond that point? What if someone has been on some kind of drug for, let us say, 3 years, 2 years, or 5 years? Are there not effects, as has happened in the past, that did not show up maybe in the first few weeks or the first few months, or the first year, or the first 2 years?

Dr. LAWRAZON. We have a great deal of evidence for long-term study and treatment in patients. As a matter of fact, each of the two other physicians appearing today before the committee has had long-term studies going in patients for up to 5 years or more.

Senator HATFIELD. Do you use primate centers to any degree in the long-term studies?

Dr. LAWRAZON. Only in toxicity. We have our major toxicity effort within our own group, within our own research laboratory.

Senator HATFIELD. Have you thought about the possibility of utilizing these primate centers to a greater extent on the basis of contract?

Dr. LAWRAZON. Yes.

Senator HATFIELD. Because here you have a controlled situation. In many of these long-term effects, you cannot have a human control situation, but you can have an animal control situation in these primate centers.

Dr. LAWRAZON. You are very right, and we are considering it. As a matter of fact, we have had preliminary discussions with the primate center just outside of New Orleans.

Senator HATFIELD. Let me ask you one other question. What kind of program or system is there for reporting side effects from the use of drugs? Every once in a while, I see something about a side effect, but I read it as something as a result of some individual having had some ill effects and having to initiate the reporting of that, and some physician more or less identifying the cause of it. Is there a system of reporting side effects by the drug manufacturers to the FDA and they in turn to the public, or what does exist in that way?

Dr. LAWRAZON. The system involves reporting of both side effects and adverse effects during the investigational stage of a new drug and after the New Drug Application has been approved. During the investigational stage, we anticipate certain side effects even before we go into the clinic as a result of the preclinical information and laboratory data that has been acquired.

Anticipating these, we also watch for anything that is extraordinary. If it is extraordinary to the degree in which it is potentially life-threatening, we report it directly to the FDA. Once the application has been approved, any adverse effects that occur which are not cited in the package circular, or any that are extraordinary and new or of a serious nature, we send this information in directly to the Food and

Drug Administration as an adverse reaction report. This is to be done, I believe, within 15 days of the time we acquire the information.

Senator HATFIELD. This is by regulation?

Dr. LAWRAZON. By regulation.

Senator HATFIELD. So that all pharmaceutical houses subscribe to or are required to follow this same procedure?

Dr. LAWRAZON. That is right.

Senator HATFIELD. Do you think it is an adequate procedure? Do you think it is an effective one at the present time?

Dr. LAWRAZON. I believe it is working fairly well; yes, sir. I think one of the problems, if I might say so, is the handling of massive amounts of data . . . we are talking about enormous amounts of information.

Senator HATFIELD. What I did understand you to say was the period of time that this system of reporting continues after the initial introduction of the drug?

Dr. LAWRAZON. As long as the drug is registered as a new drug, it will continue on for years.

Senator HATFIELD. You mean you are on a continuing research and accumulation of data and facts on the use of this drug all of the life of the drug?

Dr. LAWRAZON. It depends on which aspects of research with the new drug we are pursuing and how it relates to the reporting of adverse reactions, but the accumulation of data continues throughout the lifetime of the drug.

Senator HATFIELD. Do you have a pill—the pill? You do not manufacture the pill?

Dr. LAWRAZON. No, we do not.

Senator HATFIELD. Well, in my opinion, that is something.

Mr. GORDON. You mentioned the various studies that are going on. Are these conducted, sponsored, or directed by your company?

Dr. LAWRAZON. Yes, sir; they are all sponsored—the double-blind studies, the ones I reported. They are all under IND's.

Mr. GORDON. You talked about recent ones, the ones that are going on now.

Dr. LAWRAZON. That is correct. They are all established under the IND system and sponsored by us.

Senator HATFIELD. Could I ask you one followup question, Doctor?

Are you satisfied with the kind of reporting you are getting from physicians on their own experiences in the use of these drugs? What kind of conflict does a doctor face in possibly being fearful of malpractice charges if he reports some of most, say, erratic kinds or the most undesirable kinds of reactions? Is there an inhibition on the part of the physician, or what kind of relationship do you have on that?

Dr. LAWRAZON. I would say that one of our greatest problems, as it is in most circumstances these days, is communication. However, we have established within our research group, at least, a good working relationship with physicians so that reporting and constant surveillance of ongoing studies are handled as well as we possibly can. We are always attempting to improve this. Distance, time, these are factors. We try to minimize any delay in communications with physicians.

Senator HATFIELD. You are not really, then, fully satisfied with the kind of reporting which you now have from physicians?

Dr. LAWRAZON. I do not think we will ever be fully satisfied, sir.

Senator HATFIELD. Do you think this present lack or, let us say, this underdeveloped reporting system that exists now could become a source of difficulty for you in getting some real evaluations in some of these drugs?

Dr. LAWRAZON. They have in the past, but we have spent a great deal of time in examining the issues and rectifying the problems. I would hope that they would not.

Senator HATFIELD. There is no role of Government, then, that you see?

Dr. LAWRAZON. No; just that it is part of the requirement for adequate supervision and surveillance of the studies.

Senator NELSON. Please go ahead, Doctor.

Dr. LAWRAZON. The committee has heard much of the ARA Co-operating Clinics project and of other approaches to the development of controlled studies. When the ARA project offered the opportunity to have our new drug be the first agent employed in a complex study of this design, we were pleased. We consulted with the committee and we supported its goals, even though all previous experience with such studies indicated that no agent of demonstrated anti-inflammatory and analgesic properties had ever successfully been differentiated this way.

Mr. GORDON. I have been informed by Dr. Donald Mainland of the Cooperating Clinics Committee, that they did a trial on hydroxy-chloroquine sulfate. This was a 6-month trial using the same method as was used with Indocin, with aspirin permitted in accordance with the committee's practices. The trial showed clear cut differences between the drug and placebo.

Dr. LAWRAZON. I am not a clinic witness.

Mr. GORDON. This does not fit in with what you were just saying. You said there was no such study, or that this type of study had never shown any differentiation. This particular study apparently did. I just wanted to bring that to your attention.

Dr. LAWRAZON. Has this study been published?

Mr. GORDON. I do not know.

Dr. LAWRAZON. We are referring to the fact that a similar study was carried out with cortisone almost 10 years ago. It showed that cortisone was no more effective than the placebo. I believe there was another study that has not yet been published, to our knowledge, and that this also failed to show a difference.

Mr. GORDON. I also would like to read into the record the communication I received from Dr. Mainland on April 24, 1966, with respect to that type of study that they did. It says:

In addition to review by the editor and referees of the Journal in which the report was to be published, Dr. Mainland requested a manuscript of this report be reviewed by Dr. Stanley Shor, who has been director of the Department of Biostatistics of the American Medical Association \* \* \*. Dr. Shor was very critical and very experienced in reviewing medical journal manuscripts as exemplified by his report on the subject, "statistic evaluation of medical journal articles," volume 195, pages 41123 to 41128. Dr. Shor commented on April 18, 1966, on the indomethacin report as follows—

that is the CCC report—

"It is, I think, the type of analysis that should be kept as a reference by every clinic investigator. Many times I am asked, are there any studies that have been published that you think are really good in terms of drug trials. Of course, every

drug trial has its own bundle of problems, and it is not very useful to set up a step-by-step procedure which is to be used by all drugs in all cases. However, the analysis in this paper brings out so many important points which the usual clinical investigator is either not aware of or simply does not take into consideration that it should be required reading for all the people engaged in clinical trials. I particularly like your method of showing how observed differences could be misleading in the absence of controls. This is especially interesting in your dose response relationship near the end of the manuscript."

I ask that this be included in the record at the proper place.

Senator NELSON. Very well.

Mr. CUTLER. Could we have a copy, Mr. Gordon?

Mr. GORDON. Certainly; I shall have it Xeroxed and give it to you.  
(The documents referred to follow:)

[From Bulletin on Rheumatic Diseases, vol. 13, No. 2, October 1962, pp. 287-290]

#### HYDROXYCHLOROQUINE SULFATE IN RHEUMATOID ARTHRITIS, A SIX MONTH, DOUBLE-BLIND TRIAL<sup>1</sup>

This trial was conducted by the Cooperating Clinics Committee of the American Rheumatism Association, under the chairmanship of Dr. Charles Ragan. In attempting to create an instrument that can promptly and reliably evaluate a new and apparently promising drug, the Committee is acutely aware of the danger of a controlled trial that is inadequately planned and loosely conducted. The pseudoscientific verdict of such a trial is more misleading than the impression of a single experienced and critical clinician. A report<sup>2</sup> of the Committee's activities from 1958 through September 1961 describes the difficulties it met and the methods adopted to reduce them. Having gained experience in a pilot study ("dry run") and in a three month trial of hydroxychloroquine, the Committee decided to conduct a six month trial of the same drug, partly to obtain more experience and partly to learn more about the behavior of the drug. It recognized that there is considerable evidence that antimalarial compounds benefit certain types of rheumatoid patients to some degree under certain conditions; but it wished to know (1) whether a drug-placebo difference could be demonstrated on the available patients by the methods employed and (2) the magnitude of such a difference.

##### CRITERIA OF ADMISSION TO THE TRIAL

The subjects were to be outpatients, of either sex and any ethnic group, with classical or definite peripheral rheumatoid arthritis (A.R.A. Criteria, 1958 Revision<sup>3</sup>) which had become manifest after the sixteenth birthday and had been present for at least one year before the trial. There were to be present at the beginning of the trial at least three clinically active joints, as determined by tenderness on pressure and/or pain on passive movement. Joint swelling was not used as a criterion of eligibility but was recorded and used in assessment of progress.

Patients with certain specified diseases, such as polyarteritis nodosa, psoriasis, systemic scleroderma, ulcerative colitis and disseminated lupus erythematosus, were excluded, as were patients who, within the previous six months, had experienced pregnancy, childbirth, severe infection or a major surgical operation. Patients who were known or suspected to have ankylosing spondylitis were excluded, but it was not obligatory to screen all patients by sacroiliac radiology. Previous therapies that excluded patients were antimalarials, systemic steroid or phenylbutazone therapy within the preceding two months, and gold therapy within the preceding year, unless a full course within the year had produced no obvious effect.<sup>4</sup>

<sup>1</sup> From the Medical Statistics Unit and the Study Group on Rheumatic Diseases, New York University Medical Center. Mailing address: 112 East 19th Street, Room 1106, New York 3, N.Y.

<sup>2</sup> Mainland, D., *J. New Drugs*, 1:197, 1961.

<sup>3</sup> Ropes, M. W., et al., *Bull. Rheumat. Dis.*, 9:175, 1958.

<sup>4</sup> Probably in all clinical trials there are some implicit restrictions on the type of patient population to which the results can be generalized. Such restrictions are not easy to define and may be overlooked. In this trial, in which the primary objective was a study of the method of operation itself, it was desirable to obtain maximum and willing cooperation. Therefore it would have been unwise to insist that patients who appeared to be benefiting from another therapy be entered in the trial, or to risk the placebo treatment of patients who, in the opinion of the clinic chief or clinical observer, ought to be available for steroid therapy whenever it might appear desirable.

## THERAPY

The prescribed dosage of drug or corresponding placebo was one 200 mg. tablet four times daily. Assignment of drug or placebo by random numbers was performed at the Coordinating Center at New York University. Approximately equal numbers of drug- and placebo-treated patients were studied at each clinical center. During the trial, systemic steroids, gold and phenylbutazone or related drugs were not permitted, nor were antimalarials. Aspirin was permitted or prescribed at the discretion of the individual observers.

## METHODS OF EVALUATION

Two initial examinations were made, one week apart, and on the second visit therapy was started. Thereafter the patients were examined six times at 28 day intervals (maximum permissible deviation,  $\pm 7$  days). All observations on any one patient were made by the same observer. The following methods of assessment were used.

1. *American Rheumatism Association functional classification*,<sup>5</sup> with reference to the patient's usual occupation (recorded on each visit).

Class I—able to carry on all usual activities without handicap.

Class II—able to carry on all usual activities despite handicap of discomfort or limited mobility of one or more joints.

Class III—able to perform few or none of the usual activities or self-care.

Class IV—largely or wholly incapacitated; bedridden or confined to wheelchair, with little or no ability for self-care.

2. *Duration of morning stiffness*—estimated for an "average" or "typical" day (recorded on each visit).

3. *Number of clinically active joints*—determined by tenderness on pressure and/or pain on passive movement and/or swelling other than bony proliferation (recorded at beginning of trial again after 3 months and after 6 months).

4. *Grip strength*—determined by folded blood pressure cuff attached to mercury sphygmomanometer, with patient's arm unsupported. Read height of column maintained (not initial spurt) by squeezing. Record mean of three readings on each hand (recorded on each visit).

5. *Walking time*—the time, recorded by stop watch, required to walk 50 feet as fast as possible (without running) from a standing start (recorded at beginning of trial, again after 3 months and after 6 months).

6. *Erythrocyte sedimentation rate*—Westergren method, one hour reading (obtained at beginning of trial, again after 3 months and after 6 months).

7. *X-ray films*—postero-anterior, both hands (obtained at beginning and end of trial).

8. *Observer's overall assessment*—the observer's opinion at end of trial regarding the change in the patient's arthritis since the beginning of the trial, recorded as "better," "about the same" or "worse."

9. *Patient's impression*—recorded at end of trial in the same terms as the observer's assessment.

Undesirable signs and symptoms during the preceding four weeks were reported at each visit.

The trial extended from December 1960 through September 1961. It involved 121 eligible patients from 10 clinics (7 to 20 per clinic), including 63 on placebo and 58 on the drug.

## PATIENTS' CHARACTERISTICS AT BEGINNING OF TRIAL

Table I shows the principal characteristics recorded. The distribution by A.R.A. functional classes was: Class I-11; II-68; III-38; IV-4. Rheumatoid factor tests were reported as follows: positive—76; negative—18; doubtful—1; not investigated recently—26. In Table I the range of individual variation represents approximately the middle 90 per cent of the frequency distribution. In none of the characteristics was there any important difference between the placebo and drug-treated patients.

<sup>5</sup> Steinbrocker, O., Traeger, C. H., and Batterman, R. C., *J.A.M.A.*, 140:659, 1949.

TABLE I.—PATIENTS' CHARACTERISTICS AT BEGINNING OF TRIAL  
[41 males; 80 females]

	Median	90 percent Range
Age (years)	53	31 to 72.
Duration of disease (years)	6	1½ to 21.
Duration of morning stiffness (hours)	2	1½ to 7.
Number of clin. active joints <sup>1</sup>	23	5 to 54.
Grip strength (mm. Hg) <sup>2</sup>		
Males	95	53 to 260.
Females	96	44 to 237.
50-ft. walk (second)	14	9 to 34.
ESR (mm. in 1 hour)	40	10 to 86.

<sup>1</sup> Total possible joints (excluding hips): 66.

<sup>2</sup> 2 males and 2 females had maximum registrable strength, 260 mm. Hg.

### RESULTS

The data from 8 of the 121 patients presented problems in the analysis; e.g., one patient had received phenylbutazone from a private physician during the trial, one had fractured her hip and one had disappeared entirely. After the analysis of the data from the remaining 113 patients, the 8 problem cases were incorporated in such a way as to avoid bias in favor of the drug. The effect on the main results was negligible. In some instances, however, specific figures were not available for the problem cases; therefore the results given below are from the 113 cases, 60 on placebo and 53 on the drug. In certain analyses some cases had to be excluded; e.g., 11 in the walking test because of inability to walk or absence of lower limb lesions, and 11 in the E.S.R. records because of unreliable laboratory work at one clinic. None of the omissions are due to defective reporting by observers. All comparisons cover the whole six months of the trial.

NOTE: To avoid the statistical term "significant," with its suggestion of "importance," drug-placebo differences are stated to be "adequately accounted for by individual variation" if they would occur in more than 5 per cent of random assignments (such as were used in this trial) when there was no difference at all between treatments. On the other hand, a difference is interpreted as being "associated with the drug" if the frequency of occurrence in purely random assignments would be less than 5 per cent—2 or 3 per cent at most.

#### Total group comparisons by individual indexes

In Table II all the differences appear to favor the drug, but all could be readily accounted for by individual variation. Moreover, the two groups differ very little in the average (median) amount of change, and the individual variation is high in both groups.

TABLE II.—TOTAL GROUP COMPARISONS BY 5 INDEXES

Index	Placebo (60 patients)				Drug (53 patients)			
	Num- ber	Improved (percent)	Median change	90 percent range	Num- ber	Improved (percent)	Median change	90 percent range
Duration of morning stiffness	56	54	-1½ hour	-3 to +4½	53	66	-¾ hour	-4½ to +1½
Number of clin. active joints	60	62	-3 joints	-19 to +16	53	70	-7 joints	-32 to +6
Grip strength	56	70	+12 mm	-47 to +55	51	86	+29 mm	-17 to +123
50-foot walk	54	46	0 seconds	-6 to +14	48	50	0 seconds	-10 to +8
ESR	49	45	+1 mm	-34 to +34	42	64	-7 mm	-37 to +55

#### Subdivision by initial severity

In four indexes (morning stiffness, number of clinically active joints, walking time and E.S.R.) a much more clear-cut drug-placebo difference was found when the data from patients who were more severely affected at the beginning of the trial (a quarter to a third of the total patients) were examined separately (Table III). In the first two of these indexes the differences were clearly associated with the drug. In grip strength, the patients who were stronger initially showed the greater drug-placebo difference.

TABLE III.—COMPARISONS AFTER SUBDIVISION BY INITIAL SEVERITY

[P=placebo; D=drug]

Index	Initial severity	Number of patients		Median change in group	Percent exceeding group median		Median change in subgroup	
		P	D		P	D	P	D
Duration of morning stiffness.	3 or more hours.....	22	18	-2½ hr....	32	72	-1½ hours..	-3 hours.
Number of clin active joints.	More than 28 joints.....	18	19	-10 joints..	28	68	-6 joints..	-16 joints.
50-foot walk.....	More than 16 seconds.....	15	14	-2 seconds	27	64	0 seconds	-3 seconds.
ESR.....	More than 55 mm.....	17	13	-12 mm....	41	61	-11 mm....	-17 mm.
Grip strength.....	75 mm. Hg or more.....	34	36	+22 mm....	35	64	+14 mm....	+34 mm.

*Overall assessments*

Three methods of overall assessment showed marked differences associated with the drug.

1. *A.R.A. functional classes*—Of the patients initially in Class II, only 9 per cent of 33 who were on placebo moved to Class I, whereas 50 per cent of 30 drug-treated patients did so. (P approximately 0.001.) Migration of Class III patients to Class II showed no influence of the drug.

2. *Five point scoring system*—Each patient was given a score of one unit for an improvement in any one of the five individual indexes and the scores were then summated. (When a patient could not score on one of the indexes, e.g., through inability to walk, an adjustment was made to bring his total possible score up to 5.) Scores of 3, 4 or 5 were counted as "improvement" (Table IV). This index had shown a drug-placebo difference in the three month hydroxychloroquine trial and is to be explored further as an overall measure.

TABLE IV.—COMPARISONS BY OVERALL ASSESSMENTS

Parameter	Placebo		Drug	
	Number	Improved (percent)	Number	Improved (percent)
Advanced from class II to class I.....	33	9	30	50
5 point scores.....	57	54	53	75
Observers' assessments.....	60	35	53	64
Patients' impressions.....	60	60	53	75

3. *Observers' overall assessments*—This was not a "clinical impression" in the ordinary sense because the observers had a summary of their month by month observations; but perhaps it is the most comprehensive summing-up of a patient's progress and it is free from treatment-connected bias in a truly double-blind trial.

The patients' impressions of drug-placebo differences, considered apart from the other data, could have been accounted for by individual variation.

No patient went into remission during the trial.

*X-ray evidence*—assessment (by Dr. Josephine Wells, Columbia University) is not yet finished but an unselected sample of films from 50 patients has shown no drug-placebo difference.

*Undesirable signs and symptoms*

Table V shows that all the recorded phenomena occurred more frequently in drug-treated patients, but the placebo patients showed considerable frequencies that might have been attributed to the drug in a trial without placebo. No patient was removed from the trial because of these occurrences.

TABLE V.—UNDESIRABLE SIGNS AND SYMPTOMS

[Percentages represent patients (out of 60 placebo treated and 53 drug treated) who reported an occurrence on 1 or more visits after therapy started]

Sign or symptom	Frequency (percent)	
	Placebo	Drug
Pruritus.....	38	58
Skin rash.....	32	53
Headache.....	48	53
Abdominal pain.....	47	49
Tinnitus.....	37	47
Nausea.....	38	45
Dizziness.....	35	43
Blurred vision.....	20	43
Diarrhea.....	20	40
Anorexia.....	30	38
Stomatitis or sore tongue.....	15	30
Vomiting.....	15	23
Photophobia.....	10	13
Miscellaneous.....	63	75

*Variables other than therapy*—The samples were too small to provide sensitive tests of the relationship between the outcome of the trial and such variables as age, sex, duration of disease at start of trial, presence or absence of rheumatoid factor and differences between clinics. The data did not, however, suggest any close relationship between these variables and the improvement rates or drug-placebo differences.

#### CONCLUSIONS REGARDING DRUG EFFECTS

Three overall measures (functional class, observers' assessment and the five point scores) have shown differences in percentage frequency of improvement that were associated with the drug; and so also have certain individual indexes in patients who were severely affected at the beginning of the trial. "Association," however, does not imply causal relationship in a trial that cannot be maintained completely double-blind. It is conceivable that observers, nurses or others might have guessed at the patients' therapy from side-effects and then, probably unconsciously, they might have affected the patients' responses to questions and tests. To detect such an influence, the number of undesirable signs and symptoms reported on the final visit were compared with the observers' overall assessments and with the five point scores. No consistent relationship was found. Perhaps the test was too insensitive; but the magnitude of the percentage frequency differences in Table IV, taken along with other workers' experience with antimalarials, leaves little doubt that the drug-placebo differences were largely cause-and-effect relationships.

One must, of course, beware of accepting percentage differences found in samples of 50 or 60 patients as equivalent to what would be found in a study of much larger numbers of patients of the same kind and under the same conditions. The observers' figures for improvement were placebo—35 per cent, and drug—64 per cent, a difference of 29 per cent. Even if the patients in the trial were strictly random samples of their respective (placebo and drug) populations, all that the 29 percent could tell us would be that the true (population) difference was probably somewhere between 15 and 40 per cent.

#### SEROLOGICAL STUDIES

Sera collected from all patients at the beginning and end of the trial were sent to the Rackham Arthritis Research Unit in Ann Arbor, Michigan, for serological, chemical and electrophoretic studies. Complete pairs of sera were available from 50 drug- and 52 placebo-treated patients. We are grateful to Drs. George R. Thompson and Ivan F Duff for permitting us to summarize some of their results here prior to their own publication.

*Latex agglutination tube test*—Thirty-six drug- and 44 placebo-treated patients had positive tests initially. In 7 drug and 2 placebo-treated patients the tests became negative. When changes in titer of more than one tube up or down were examined, the following contrasts were observed: in the 50 drug-treated patients, a fall in 10 and a rise in 3; and in the 52 placebo patients, a fall in 5 and a rise in 6. Although these differences could have been accounted for by individual variation, it should be noted that they are in agreement with results

reported for the sheep cell agglutination test following administration of chloroquine<sup>6,7</sup> and of gold.<sup>8</sup> There was no obvious relationship between the latex test results and the clinicians' overall assessments.

*Changes in serum albumin*—Electrophoretic analyses showed a rise in patients who were reported to be clinically better or unchanged, and a fall in those reported as worse. The difference could not be accounted for adequately by individual variation. The changes did not differ markedly between the two treatment groups.

*Changes in serum gamma globulin*—There was a return toward normal in the drug-treated, but not in the placebo patients.

#### PARTICIPATING CENTERS

Lack of space prevents listing the 55 persons (clinic chiefs, observers and nurse-secretaries) who contributed to this trial. The 11 participating centers were: Rackham Arthritis Research Unit, University of Michigan, Ann Arbor; National Institute of Arthritis and Metabolic Diseases and Georgetown University Medical Center, Bethesda and Washington, D.C.; Massachusetts General Hospital, Boston; University of Illinois, Chicago; Southwestern Medical School, Dallas; University of California and Veterans Administration Hospital, Los Angeles; University of Tennessee, Memphis; Jackson Memorial Hospital, Miami; Presbyterian Hospital, New York; University of Pennsylvania, Philadelphia; and University of California, San Francisco.

#### ACKNOWLEDGMENTS

The project was supported by Grant A-3252 from the National Institutes of Health, U.S. Public Health Service, and by funds from The Arthritis and Rheumatism Foundation for x-ray expenses. The Committee is indebted to Winthrop Laboratories for generous supplies of the drug (Plaquenil) and placebo, and for cooperation in the special labeling and dispatching of the compounds.

The co-authors wish to express their indebtedness to their former colleague, Miss Lee Herrera for her invaluable contributions to this work. She participated in all the activities of the project until October 1961 when she moved to California.

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New York, N.Y.

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#### ASPIRIN IN RHEUMATOID ARTHRITIS, A SEVEN-DAY, DOUBLE-BLIND TRIAL— PRELIMINARY REPORT

The time honored place of salicylates in the therapy of the rheumatic diseases as well as their postulated mode of action is being reappraised by many investigators today. This preliminary report of a therapeutic trial of aspirin points up effectively the pitfalls, the tremendous problems and great effort involved in carrying out such clinical studies in order to obtain data which can be meaningfully interpreted. Certainly salicylates are most useful compounds but contrary to the claims of some advertisers their true effectiveness and action has yet to be determined. Attention is called to Dr. Mainland's invitation for readers to submit questions and suggestions regarding this trial to him.

—THE EDITOR.

This trial was conducted by the Cooperating Clinics Committee of the American Rheumatism Association, under the chairmanship of Dr. Charles Ragan. After conducting double-blind trials on an antimalarial compound<sup>1,2</sup> and a seven-day variability study<sup>3</sup> on 499 patients without change in their assigned therapies,

<sup>6</sup> Freedman, A., and Steinberg, V. L., *Ann Rheumat. Dis.*, 19:243, 1960.

<sup>7</sup> Popert, A. J., Meijers, K. A. E., Sharp, J., and Bier, F., *Ann. Rheumat. Dis.*, 20:18, 1961.

<sup>8</sup> Research Subcommittee, Empire Rheumatism Council, *Ann. Rheumat. Dis.*, 19:95, 1960.

<sup>1</sup> Mainland, D., *J. New Drugs*, 1:197, 1961.

<sup>2</sup> Mainland, D., and Sutcliffe, M. I., *Bull. Rheumat. Dis.*, 13:287, 1962.

<sup>3</sup> Cooperating Clinics Committee of the American Rheumatism Association, *Arth. and Rheumat.*, 8:302, 1965.

the Committee turned its attention to the scarcity of well-documented information on the clinical effects of aspirin. It decided to study the changes in manifestations of disease activity in patients who were continued on their previously assigned antirheumatic therapies, but were assigned strictly at random to aspirin in a fixed rather high dosage or to placebo, in approximately equal numbers, and were studied by the double-blind technique. In order to avoid excessive distress to patients, and a risk of breakdown of the trial, the period was restricted to seven days.

#### CRITERIA OF ADMISSION TO THE TRIAL

The patients were to be outpatients (or domiciliary hospital patients), of either sex and any ethnic group, with "classical" or "definite" peripheral rheumatoid arthritis (A.R.A. Criteria, 1958 Revision<sup>4</sup>) which had become manifest after the sixteenth birthday. In addition to the 20 exclusions in the A.R.A. Criteria, patients were not to be admitted if they had experienced severe infection or major surgical operation within one month before the start of the trial, or if they had a history of toxic reactions to aspirin. Patients who were known or suspected to have ankylosing spondylitis were to be excluded, but it was not obligatory to screen all patients by sacroiliac radiography.

#### THERAPY

The drug, acetylsalicylic acid, was administered in capsules, each capsule containing 7.5 grains (approx. 0.5 gm.) and the prescribed dose of drug or corresponding placebo was 2 capsules 4 times a day for 7 days (total daily dose = 60 grains = 3.9 gm.). Assignment of drug or placebo was performed by random numbers at the Biometrical and Coordinating Center. Except for these assignments, patients were allowed to be on any (or no) therapy for rheumatoid arthritis, but it was stipulated that, if possible, no change be made in the type of therapy during the two week preceding the trial or during the trial itself, and also that dosage changes, especially of corticosteroids, be minimal during the trial. Patients were urged to refrain from aspirin and other salicylates during the week of the trial. Details of types and dosages of all therapies were recorded in the data sheets for use during analysis. The trial extended from April 5 through November 14, 1963.

#### METHODS OF EVALUATION

All observations at the initial and final examination (Day 1 and Day 8) were to be made by the same observer who was to have at least the rank of clinical fellow. The maximum allowable departure from the 7-day interval was  $\pm 1$  day. The following assessments were made in both examinations:

1. *American Rheumatism Association functional classification<sup>5</sup>* with reference to the patient's usual occupation.

2. *Duration of morning stiffness*—estimated for an "average" or "typical" day.

3. *Grip strength*—determined by folded blood pressure cuff attached to mercury sphygmomanometer, with patient's arm unsupported. Inflate initially to 20 mm. Hg. Read height of column maintained by squeezing (not initial spurt). Record three successive readings on each hand.

4. *Walking time*—the time required to walk a straight continuous distance of 50 feet as fast as possible (without running) from a standing start.

5. *Number of clinically active joints*—determined by any one of the following: tenderness on pressure, pain on passive movement, swelling other than bony proliferation. Recorded also were heat, redness, ankylosis (determined by clinical examination) and subcutaneous nodules.

6. *Erythrocyte sedimentation rate*—Westergren method; anticoagulant, 3.8% sodium citrate; one hour reading.

7. *Patient's assessment*—the patient's impression regarding his arthritis, recorded as "good," "fair" or "poor"; and as "better," "about the same" or "worse" in comparison with his condition one week previously.

8. *Observer's overall assessment*—recorded in the same terms as the patient's assessment, taking into account not only the impressions gained from the measurement methods (without referring to Day 1 data sheets), but any other available information.

<sup>4</sup> Ropes, M. W., et al., Bull. Rheumat. Dis., 9:175, 1958.

<sup>5</sup> Steinbrocker, O., Traeger, C. H., and Batterman, R. C., J.A.M.A., 140:659, 1949.

*Blood salicylate levels* were determined on Day 1 and Day 8 at six clinics by the method of Brodie, Undenfriend and Coburn.<sup>6</sup> The interpretation of these data is complicated by the variability of the intervals between the last dose of aspirin on Day 8, the time of clinical examination and the withdrawal of blood for salicylate determination. The more detailed report will include this topic.

The data sheets called for the reporting of *undesirable signs and symptoms*, but no check list was provided. Expenditure of much time on this inquiry did not appear to be justified because no valid population estimate of frequencies could be made from a group that was partly selected by exclusion of salicylate reactors.

#### PATIENTS' CHARACTERISTICS

From the 492 patients who were entered in the trial, the data of 51 (28 on placebo and 23 on aspirin) were omitted from the analysis for the following reasons: ineligible by protocol, 19; drop-outs or late for final examination, 14; change in basic therapy, 15; change in observer, 3. If this had been a trial of a new drug it would have been necessary to handle the data from the drop-outs and late attenders in such a way as to avoid bias in favor of the drug. This hardly seemed necessary, at least in a preliminary report on experiences with aspirin.

The remaining 441 patients were considered eligible in all respects, including the interval between assessments (9 were one day late, 1 was one day early). They were provided by 11 clinics (18 to 86 per clinic). Assigned to placebo: 223; assigned to aspirin: 218. Males: 131; females: 310. Median age: 53; range (middle 90 per cent): 30 to 73. Median duration of disease: 7 years; range (middle 90 per cent): 1-27 years.

#### THERAPIES

The basic therapies with numbers of patients assigned to placebo (P) and aspirin (A) were as follows: Corticosteroids (P, 59; A, 55); Salicylates (P, 100; A, 93); Antimalarials (P, 14; A, 17); Miscellaneous, i.e., combinations of therapies and some patients who at the beginning of the trial were receiving no anti-rheumatic therapy (P, 50; A, 53). Thirty-one patients were receiving indomethacin, usually along with another therapy. Except in the salicylate group, all these patients were maintained on their basic therapies during the trial.

In order to permit a search for relationships between intake of the trial therapy and the outcome of the trial, patients were classified rather arbitrarily as "on schedule" if they met all the following criteria: (1) at least 32 capsules during the 5 days following the day of the initial examination; (2) at least 8 capsules on the day preceding the day of the final examination, or 6 capsules if the only dose missed was the breakfast dose; (3) at least 2 capsules on the day of the final examination.

The 117 patients (28% of the P patients, 25% of the A patients) whose reported dosage failed to meet one or more of these criteria were classified as "not on schedule." There was little difference in the proportions of these among the various therapy groups. The data were analyzed as a whole, and also in "on-schedule" and "off-schedule" groups separately. The results from the total 441 patients are shown here, because when a pronounced placebo-aspirin difference in outcome occurred, it did so in spite of the incomplete dosage of some patients.

#### COMPARISON OF AVERAGE CHANGES IN FIVE MEASURES OF DISEASE ACTIVITY

Table 1 shows the placebo-aspirin contrast in patients who in the initial examination were recorded as having greater than zero readings in the respective measures of disease activity, because the inclusion of initially "inactive" patients would tend to damp the contrast between the two agents. To estimate how frequently the drug-placebo contrasts in the table would occur solely as the result of the random assignments, the data were arranged in fourfold tables (placebo versus aspirin; improved versus not improved, i.e., deteriorated or unchanged), and the chi-square test (with Yates' correction) was applied. In all measures except morning stiffness the differences would rarely occur in random assignment (P values from chi-square less than 0.01). In morning stiffness the P value was 0.12; which means that, even if there were no difference

<sup>6</sup> Hepler, O. E., Manual of Clinical Laboratory Methods, Charles C. Thomas, Springfield, Illinois, 1953.

in the effect of placebo and aspirin on this measure of activity, differences as great as the observed difference, and greater, would have been produced by the randomization alone.

These results, therefore, appear to have provided a clear demonstration of aspirin effect on all the measures except morning stiffness.

TABLE 1.—COMPARISONS BY 5 MEASURES OF DISEASE ACTIVITY

[Impr. (I.)=improvement. Deter. (D.)=deterioration. N.C.=no change.]

Measure of activity	Placebo					Aspirin				
	Number in group	Impr. (percent)	N.C. (percent)	Deter. (percent)	Median change	Number in group	Impr. (percent)	N.C. (percent)	Deter. (percent)	Median change
Morning stiffness—	198	33	23	44	0	184	41	32	27	0
Clin. active joints—	220	38	10	52	1 jt. D	216	56	9	36	1 jt. I.
Grip strength:										
Male-----	61	31	0	69	15.5 mm. D	58	64	0	36	5.5 mm. I.
Female-----	152	38	1	61	7.5 mm. D	153	59	2	39	7.5 mm. I.
50-foot walk-----	214	41	13	47	0	209	55	16	29	0.5 sec. I.
E.S.R.-----	214	30	5	65	3 mm. D	213	51	8	41	1 mm. I.

Note: Patients excluded: (a) Reported absence of disease activity on initial examination: morning stiffness 55; joints 4; grip 10 males and 4 females. (b) Inability to perform test: walking 18; grip 1 male and 1 female. (c) Imperfect data etc.: morning stiffness 4; joints 1; grip 1 female; E.S.R. 14.

Of particular interest was the question whether the salicylate group, about half of whom were suddenly deprived of their basic therapy for the seven days of the trial, showed a larger placebo-aspirin difference than did the other basic therapy groups—particularly a greater frequency of deterioration when on placebo than the corticosteroid group. All the basic therapy groups were analyzed with reference to this question, but no consistent difference could be found attributable to the salicylate deprivation in those who had been on that therapy at the beginning of the trial. It is possible, however, that the conditions of the trial were not suitable to demonstrate such an effect, owing to the variable and uncontrollable time intervals between the clinical examination and the preceding dose of aspirin.

#### EXTENT OF CHANGE IN DISEASE ACTIVITY

Table 1, showing overall percentage frequencies and averages, has restricted significance because:

1. A drug-placebo difference in the frequency of improvement may be large but of little practical value if the amount of the improvement is small.
2. The averages of the gains and losses, and the drug-placebo differences in these averages, are trivial; but in certain subgroups the differences may be large. (The records of voluntary aspirin consumption by placebo patients did not suggest that this was the cause of the small size of the differences.)
3. The lack of any conclusive drug-placebo difference in the effect on morning stiffness may have been due to the inclusion of subgroups that were not likely to show much change in a period of seven days.

Much more informative are statements about the ranges of improvement or deterioration, and the Seven-day Variability Study has shown that these differ according to the initial (Day 1) level of activity. In that study those levels were divided, for each measure separately, into classes from A (the mildest) to J (the most severe), each class containing as nearly as possible 10 percent of the total 499 patients in the study.

As examples, Table 2 shows the application of the Variability-Study classification to certain of the data in the present study. In addition to the display of the extent of change, the sub-classification provides a method for increasing the sensitivity of comparisons in drug trials. Thus, although the analysis of the total data showed no convincing drug-placebo difference in the morning stiffness change, the figures in Table 2 show that, when allowance is made for the amount of stiffness recorded on Day 1, the drug-placebo difference becomes more obvious. For example, of the patients who started with 5–25 minutes of morning stiffness, 26 percent of placebo patients reported an hour or more on Day 8, whereas only 5 percent of the aspirin patients reported that amount of deterioration. A later report will show the general application of this simple method of increasing the sensitivity of a trial.

TABLE 2.—EXAMPLES OF RANGE OF VARIATION WITH ALLOWANCE FOR SEVERITY AT INITIAL EXAMINATION

[P=placebo; A=aspirin; VS=variability study; m.t.=more than; l.t.=less than]

Severity Class at Init. Exam.	Number in group			Impr. to:	Percent of number in group			Det'n. to:	Percent of number in group		
	P	A	VS		P	A	VS		P	A	VS
<b>Morning stiff:</b>											
A. zero	23	32	57	zero	5	10	10	m.t. 25 min.	22	6	9
B. 5-25 min.	19	21	20	l.t. 30 min.	6	11	5	m.t. 55 min.	26	5	10
I. 3.75-4.75 hr.	17	18	19	l.t. 2.75 hr.	21	19	4	m.t. 4.75 hr.	53	1	721
J. 5 hr.-all day	24	21	48								
No. of clin. active jts.:								m.t. 8.	18	0	7
A. 0-3	17	12	44	l.t. 4	15	33	39	m.t. 8.	31	11	8
B. 4-5	13	9	36	l.t. 20	0	8	9	m.t. 36	36	25	24
I. 30-36	14	24	45	l.t. 25	4	6	9				
J. 37-66	25	18	35								

Note: Improvement or deterioration implies change from one class to another.

## OVERALL ASSESSMENTS

Table 3 shows the placebo-aspirin contrast in relation to the A.R.A. functional classification. There appeared to be a slightly greater tendency to improve in the drug-treated than in the placebo patients, more especially in the less disabled patients; but it will be noted that numerous changes of class were recorded in the Variability-Study patients who were maintained for one week on their accustomed therapies.

TABLE 3.—COMPARISONS BY ARA FUNCTIONAL CLASSES

[P=placebo; A=aspirin; VS=variability study]

Class at initial examination	Treatment	Number in class (N)	Class at final examination (percent of N)			
			I	II	III	IV
I	P	11	55	36	9	
	A	17	71	29		
	VS	36	81	17	3	
II	P	121	1	86	12	2
	A	125		94	6	
	VS	205	0.5	96	4	
III	P	80		9	86	5
	A	67		12	88	
	VS	152		5	94	1
IV	P	5				100
	A	7				100
	VS	17			12	88

From Table 4 it would appear that the patients were somewhat more optimistic than the physicians regarding improvement in general and regarding the benefits of the trial therapy; and a similar observation was made in an anti-malarial trial. It appears, also, however, that the patients were more pessimistic regarding deterioration—that they were more ready to report change, in one or other direction, than the physicians. (A more detailed examination of such contrasts is being made in the data from the Seven-day Variability Study.)

TABLE 4.—OBSERVERS' AND PATIENTS' ASSESSMENTS

[Numbers of patients: Placebo, 223; aspirin, 218]

Assessors and therapies	Changes from initial to final examination (percent of pts.)		
	Improved	About the same	Worse
Observers:			
Placebo	17	48	35
Aspirin	31	54	15
Patients:			
Placebo	23	33	44
Aspirin	45	36	19

## FURTHER ANALYSES

Many questions, in addition to those discussed in this report, have been applied to the data from this trial, such as the question of the interrelationships of cumulative effect, recency of last dose and amounts of aspirin consumed—an attempt to see whether the trial could give any clue to an "optimum" aspirin regimen. However, it seemed desirable at this stage to present an overall view, as an invitation to readers to submit questions and suggestions that would help in the preparation of the more detailed report.

## PARTICIPATING CENTERS

Lack of space prevents listing the 46 observers and about 16 study-secretaries who contributed to this trial. (Study secretaries did not contribute patient assessments as some of them did in the Seven-day Variability Study.) The 11 participating centers were: Southwestern Medical School, Dallas; State University of New York, Downstate Medical Center, Brooklyn; University of Illinois, Chicago; University of California and V.A. Hospital, Los Angeles; Massachusetts General Hospital, Boston; Jackson Memorial Hospital, Miami; Rackham Arthritis Research Unit, University of Michigan, Ann Arbor; N.I.A.M.D. and Georgetown University Medical Center, Bethesda and Washington, D.C.; Presbyterian Hospital, New York; University of California, San Francisco; University of Tennessee, Memphis.

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**Senator NELSON.** Please go ahead, Doctor.

**Dr. LAWRASON.** We doubt whether even the authors of this tentative, exploratory, and hopeful experimental design, with all of the complex statistical loose ends that remain to be tied up, would hold it up to the world as a finished and refined tool of biostatistics and control.

Let me make it clear that we at Merck are in no way opposed to the intense desire of experts in rheumatology to take steps forward in clinical design. However, we do not accept the validity of the co-operating clinics study presented to this committee last week as a measure of the value of indomethacin in medical practice. We do not believe a wholly satisfactory double-blind study for demonstrating the effect of a drug in treating rheumatoid arthritis has yet been designed.

From what we know today, no drugs used in rheumatoid arthritis get at the cause of the disease, nor do they appear to halt its ultimate progression. Thus we are talking about drugs which will only give relief of symptoms. Much of this can be determined only by the patient and his physician. At this state of our knowledge there are no really good objective measurements or tests. Those we have, at best, are very crude. The rheumatoid patient manifests no objective laboratory parameters, such as the blood sugar of the diabetic, which the physician can point to and which enable him to know if the patient is improving.

As you know, aspirin has been the backbone of drug therapy in the rheumatoid patient for many years. Therefore it is natural that indomethacin would be compared with aspirin in rheumatoid arthritis, just as any new drug would be compared to an accepted standard therapy of the day. Aspirin is generally accepted by both the medical and lay public as safe. However, there is a great deal of history with aspirin which has never been written. Only in recent years has this drug come under closer scrutiny. In thinking about aspirin, one finds that it really is two drugs—the one that most people take for minor aches and pains in one-, two-, or three-tablet doses, and the second a drug which must be taken in massive doses up to 20 or more tablets (4 to 8 grams a day) to effect a therapeutic benefit in a disease such as rheumatoid arthritis.

In the case where only a few tablets are taken occasionally, as needed, there are few side effects. Most people are able to tolerate aspirin in these amounts, but even with these small doses there are patients who experience gastrointestinal irritation.

However, when one approaches the therapeutic doses of aspirin needed to treat rheumatoid arthritis, there are definite side effects—some very similar to those with indomethacin—which need to be watched carefully by patient and physician. Many patients either cannot tolerate these high doses of aspirin or just will not swallow that many tablets.

On the other hand, most rheumatoid patients who can tolerate aspirin will take it whether it is prescribed or not. If they respond to aspirin and the pain disappears, no further medication, no matter how effective, can make that pain disappear any further. If motion of a joint is allowed up to its maximum by aspirin, then indomethacin, phenylbutazone, or the steroids are unlikely to increase that motion any further. If grip strength, swelling of a joint, and inflammation, for example, have improved in a patient who responds to aspirin, an additional drug, no matter how effective, would probably not provide further improvement in the physical status of the patient.

Although we cooperated in setting up the cooperating clinics study, we did not participate in the design of the study—this was up to the committee. However, I understand there were wide differences of opinion on the study design within the committee itself, particularly with respect to whether or not those patients who were to receive indomethacin should continue to receive aspirin, in the amount the patients desired, as a basic background medication. Obviously the majority of the patients included in the study were responsive to aspirin, and it was decided to allow them to continue to take it. Whether this was the right decision is a matter of opinion, but for the reasons I cited earlier I am not surprised that neither these patients nor the physicians could determine the effect of a second active drug that was being given on top of an already "treated" patient. These studies may not have shown that indomethacin is an effective drug in rheumatoid arthritis by the rigid criteria used, but neither have they shown that it is ineffective. They show nothing as to the effectiveness of indomethacin in patients who do not respond to aspirin or cannot tolerate it in large doses. They do show that during treatment with indomethacin many patients were able to decrease the amount of aspirin they were taking, and when indomethacin was discontinued some of

the patients experienced some degree of clinical relapse. Some statisticians would consider this to be evidence of activity, but the committee chose not to accept these factors as criteria of effectiveness.

The study has yet to be designed which all would agree is the ideal format for a controlled study of such agents. Some double-blind studies were included in our original indomethacin submission to the FDA, and you have heard testimony in criticism of their structure. Dr. Mainland has stated that his study is part of a continuing, long-range effort to eliminate the unreliable factors and variables. More recently, we have been involved with the further development and design of double-blind studies. Many of these are being carried out. But here, too, it is impossible to say whether the principles underlying these studies will be generally accepted as satisfactory.

During the coming years, I am convinced, controlled clinical methodology will be developed so that truly objective data will result. As physicians in medical research at Merck, this is our job and our effort is dedicated to this end. However, it should be recognized that the clinical sciences have not yet reached the scientifically controlled state that has been attained in the laboratory. The patient is not and can never be the exact counterpart of a highly inbred, genetically and environmentally controlled laboratory animal.

If we had to do our clinical research over again with indomethacin, we would do it the same way, by first going to the expert. We would subsequently supplement our basic clinical evaluation with the best double-blind control studies we could devise. This, in fact, is what we are doing today as we take a new anti-inflammatory drug to the clinic. But so long as we do not yet know of a wholly satisfactory double-blind method of proving effectiveness for drugs used to treat rheumatoid arthritis, we do not believe there is any medical basis for postponing the introduction of a drug experts believe to be valuable.

The question of the safety of indomethacin has also been raised. It is important to distinguish between safety for use as contrasted with side effects experienced during use of the drug. The issue of safety deals with the potential threat of serious, life-threatening consequences. The issue of side effects deals with sometimes bothersome, sometimes annoying effects which are not in themselves of serious potential.

These issues have been grouped together in the discussion of indomethacin. In the resulting confusion, the major point—that most of the side effects of indomethacin are of a minor or manageable nature—has been lost. Many disappear in a short time with continuation of the medication or an adjustment of dose. Only 10 to 15 percent of all patients receiving the drug have to discontinue it because of side effects or reactions. In rheumatoid patients the incidence of patient intolerance appears to be greater than in patients with other forms of arthritis. But this is not surprising. It is well known that patients with rheumatoid arthritis have a greater sensitivity or a lower threshold to the adverse effects of many drugs, for reasons which are not known. It should be pointed out also that most of such patients are on multiple drug therapy. This, together with the vagaries of the disease itself, often sets the stage for higher incidence of adverse drug effects.

Sufficient clinical experience was accumulated with indomethacin over the years of investigation before its approval by FDA to assure

its safety for use as directed. I can assure this committee that we would not have requested consideration for approval of this drug if we had thought it was not safe.

The final overall assessment of safety can only be assured after extensive experience. For example, aspirin and related compounds which have been used for over 50 years are even now being reassessed with regard to their potential long-term effects on the kidney.

Information on the safety of indomethacin is outlined in the official product circular. So long as the physician is aware of the effects that have been reported—those that appear more frequently and those only rarely noted—we believe it can be prescribed with the proper assurance that the potential risks can be weighed against the benefits to be obtained.

We are proud of indomethacin. We know through personal experience what it means to many, many people. I am confident, looking ahead, that the scientific teams at Merck that produced indomethacin will develop further advances as they continue to search for the causes of these crippling diseases.

I will be happy to answer your questions.

Senator NELSON. Thank you, Dr. Lawrason. The committee appreciates very much your testimony for our record.

Senator Hatfield?

Senator HATFIELD. I have just one question, Doctor.

On page 6, you were saying in the third full paragraph :

We do not believe a wholly-satisfactory double-blind study for demonstrating the effect of a drug in treating rheumatoid arthritis has yet been designed.

On page 10, in talking about your clinical research, you say :

We will subsequently supplement our basic clinical evaluation with the best double-blind control studies we could devise.

I do not quite understand what the hangup is on devising or having now made effective double-blind studies. Why is it so difficult? Why do we not have it now and why do you feel you can devise one that has not yet been done?

Dr. LAWRAZON. One of the problems of the studies with rheumatoid arthritis involves the quantification of the subjective measurements; that is, measurement of response in the patient. We do not believe, as I stated, that there is yet an ideal format for design of a double-blind, controlled study. Dr. Mainland and his group in the cooperating clinics point out themselves that their efforts in this direction and their studies with indomethacin are part of a long-term effort to design a truly controlled and adequate study. But we are also in the same process. In the 100 or more such studies that we have developed over the past 2 years and are ongoing now, not all are the same. We do not claim to have the ultimate design. But this is our purpose and this is our job, to find the very best study design that can give objective measurements and results.

Senator HATFIELD. How many drugs are tested by the double-blind study? How broadly used is this technique?

Dr. LAWRAZON. Oh, this is a widespread control method, using the double-blind. It is particularly effective in getting rid of physician or patient bias where measurement is in part subjective. Some diseases are easily studied this way and some are not.

**Senator HATFIELD.** Should all the drugs be subjected to this kind of test before they are put on the market?

**Dr. LAWRAZON.** Yes, to the extent that they can. But in studying a diuretic, for example, the double-blind is really not necessary to determine whether or not there has been a diuresis within a patient, increase in urine volume.

**Senator HATFIELD.** What criteria do you use in determining when to use this double-blind study, on which drug, and when not to?

**Dr. LAWRAZON.** In those diseases where there are truly objective measurements—for the most part laboratory measurements, or objective signs within the patient of changes that take place, whether it be with the electrocardiogram or other techniques—the double-blind is of only ancillary and confirmatory value. It is where observations are being made by the physician and patient, where possible bias is interjected, that the double-blind serves the greatest purpose.

**Senator HATFIELD.** Thank you, Mr. Chairman.

**Mr. CUTLER.** Mr. Chairman, could I supplement that for a moment? When Dr. O'Brien was testifying, he construed the 1962 Drug Amendments as requiring double-blind studies to prove effectiveness in all future drugs. We have prepared a memorandum on the legislative history of the 1962 amendments, including both the term, "adequate and well-controlled," and the term, "substantial evidence." We would like to submit this memorandum for the record, if we could. It shows that Congress does not believe double-blind tests are essential for "substantial evidence"—that the Congress was well aware that for some diseases and drugs there were at that time no satisfactory double-blind tests.

With respect to "substantial evidence," one of the very illustrations given at the time was the case of rheumatoid arthritis, where doctors continued to disagree as to which drug was the preferred drug, if any, for treating the disease.

**Senator NELSON.** That memorandum will be accepted for the record.

(The document referred to follows:)

**LEGISLATIVE HISTORY  
OF THE  
DRUG AMENDMENTS OF 1962**

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**MEANING OF "SUBSTANTIAL EVIDENCE" AND "ADEQUATE AND WELL-CONTROLLED INVESTIGATIONS" AS USED IN SECTION 505(d)(5) OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT.**

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Under the Drug Amendments of 1962, Section 505(d) of the Federal Food, Drug, and Cosmetic Act was amended to include a new "effectiveness" test with those which a new drug application must pass before it is approved.

This test is set forth in Section 505(d)(5), which provides that the Secretary shall issue an order refusing to approve a new drug application if he finds that:

"[E]valuated on the basis of information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof. . ." Sec. 505(d), Federal Food, Drug, and Cosmetic Act, as amended, 21 U.S.C. 355(d).

If the Secretary finds that the above provision, and others, do not apply, "he shall issue an order approving the application."

The 1962 Amendments also added the following definition of the term "substantial evidence":

"[T]he term 'substantial evidence' means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or the proposed labeling thereof." *Ibid.*

There has been some discussion in these hearings about the meaning of the terms "substantial evidence" and "adequate and well-controlled investigations" which were introduced by the 1962 amendments.

The testimony of Dr. William M. O'Brien has particularly focused upon these statutory terms. Dr. O'Brien, in his prepared statement at page 2, stated that:

"The 1962 Kefauver-Harris amendments specifically stated that a manufacturer must support claims of efficacy of a drug with 'substantial evidence.' The law defines this as 'adequate and well controlled investigation by experts qualified by scientific training and experience to evaluate effectiveness.'

"I define the word control as a standard of comparison for checking inferences in an experiment—in other words, in testing a drug one group is treated, and its response is compared to the response of an identical group which receives a standard of comparison—a standard treatment or a dummy (placebo). I believe this was the exact intent of Congress in the 1962 amendments. . . ."

Furthermore, at page 5 of his prepared testimony, Dr. O'Brien stated that:

"The only scientifically sound method for drug testing is the controlled double blind trial which eliminates both positive and negative bias and uses a comparison—either a placebo or a standard drug."

Dr. O'Brien's views on the meaning of the pertinent statutory terms were underscored in his oral testimony before this committee, in response to a question by Mr. Gordon.

"Mr. GORDON. Is it your opinion, then, as I understand it, that before a drug is approved by the FDA, controlled double blind studies should be conducted by objective sources? Is that correct?"

"Dr. O'BRIEN. Well, apparently it is not only my opinion but this is what the 1962 amendments said. . . ."

Although Dr. O'Brien conceded in his oral testimony that the 1962 amendments did not specifically require double blind investigations, it is apparent that Dr. O'Brien reads the statutory terms "adequate and well-controlled investigations" as synonymous with, and only with, controlled double blind studies. Dr. O'Brien also concludes that "substantial evidence" can only be produced by controlled double blind studies.

The words in the 1962 amendments of course do not state so precisely what constitutes an adequate and well-controlled investigation. We submit that the lack of such exactitude in the statute was deliberate, and that Congress intended flexibility in interpretation of the statutory terms.

As this submission will show, Congress was well aware of several important points when it enacted the terms "substantial evidence" and "adequate and well-controlled investigations" in 1962. Throughout the legislative debate, it was clear that these terms could have different content, depending upon the kind of disease under consideration. Rheumatoid arthritis received particular attention as a disease about which there is great dispute as to proper methods of diagnosis and treatment. The professional witnesses who testified in the Senate and House hearings did not suggest that there was any particular or exact way to measure the effectiveness of any particular drug. The entire course of the hearings instead established that a wide range of adequate and well controlled investigations and of professional opinion about what they prove can exist with regard to any drug, and that the 1962 amendments were not intended to require an either-or choice between differing schools of thought.

#### LEGISLATIVE HISTORY

As introduced by Senator Kefauver on April 12, 1961, S. 1552 would have required the Secretary to refuse to approve a new drug application if he had insufficient information to determine whether the drug is "efficacious in use" under the conditions prescribed, recommended, or suggested in the proposed

labeling. 107 Cong. Rec. 5638. The original Senate bill did not consider the quantum of evidence necessary to establish sufficient information as to "efficaciousness," nor did it consider the manner in which such evidence should be assembled for presentation to the Secretary.

#### "SUBSTANTIAL EVIDENCE"

During the Senate hearings on S. 1552, the issue of the amount of evidence which would be sufficient to allow the Secretary to determine "efficaciousness" was thoroughly considered.

On July 19, 1962, after the Senate hearings on S. 1552, the Senate Committee on the Judiciary reported out a revised bill. At that time, the previous language regarding "efficacious in use" was amended to provide that the Secretary should refuse to approve a new drug if:

[T]here is a lack of substantial evidence (including clinical evidence), supported by investigations of experts qualified by scientific training and experience to evaluate the effectiveness of drugs, that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof . . .

The thorough debate on the issue of what would satisfy "substantial evidence" of effect resulted in a firm consensus, which is illustrated in the Senate Report.

"The term 'substantial evidence' is used to require that therapeutic claims for new drugs be supported by reliable pharmacological and clinical studies. When a drug has been adequately tested by qualified experts and has been found to have the effect claimed for it, this claim should be permitted even though there may be preponderant evidence to the contrary based upon equally reliable studies. There may also be a situation in which a new drug has been studied in a limited number of hospitals and clinics and its effectiveness established only to the satisfaction of a few investigators qualified to use it. There may be many physicians who would deny the effectiveness simply on the basis of a disbelief growing out of their past experience with other drugs or with the diseases involved. Again, the studies may show that the drug will help a substantial percentage of the patients in a given disease condition but will not be effective in other cases. What the committee intends is to permit the claim for this new drug to be made to the medical profession with a proper explanation of the basis on which it rests.

"In such a delicate area of medicine, the committee wants to make sure that safe new drugs become available for use by the medical profession so long as they are supported as to effectiveness by a responsible body of opinion.

"In his testimony supporting new authority for the Food and Drug Administration to pass on the effectiveness of new drugs before they are marketed, Secretary Ribicoff said that questions of 'relative efficacy' are not here involved, and that the requested authority 'would not require a showing of relatively greater efficacy than that of other drugs' (hearings, pt. 5, p. 2585)." S. Rep. No. 1744, 87th Cong., 2d Sess., p. 16.

The views of Senators Dirksen and Hruska, in the same Senate Report, confirm the view that substantial evidence can be less than preponderant evidence, and that room for minority opinions should exist.

"We wish to augment the discussion of the effectiveness of drugs as now provided for in the majority report. Two quotations from the Senate hearings on S. 1552 are especially notable. Eugene N. Beesley, president of Eli Lilly & Co., and chairman of the Pharmaceutical Manufacturers' Association, in his testimony before the Senate Antitrust and Monopoly Subcommittee at page 1998 stated:

"Also, it is our understanding that the manufacturer would be required to provide only substantial evidence that a drug produces the effects claimed for it. He would not be expected to prove that scientific opinion was unanimous, or even preponderant, in supporting the effectiveness of a drug. Thus, if a number of tests by competent clinicians show that in well-conducted clinical trials a drug produced the claimed effect on their patients, the drug would not be barred simply because other tests did not produce the identical results with different patients. In other words, a drug should be made available for the benefit of those patients for whom the individual physician thinks it would be useful.

"In the entire realm of medical science nothing is more difficult and more subject to honest differences of competent opinion than the determination of the therapeutic merits of drugs in human beings. Experts have sharply opposed

views concerning the proper treatment of many common diseases, and each school of thought has a strong champion. Many highly qualified physicians are convinced of the value of corticosteroid drugs in relieving rheumatoid arthritis; there are others who prefer aspirin; still others are proponents of a variety of other treatments . . . ."

"At the completion of Mr. Beesley's statement, Senator Kefauver agreed with Mr. Beesley's determination of effectiveness in the following language found on page 2007 of the printed hearings.

"'You agree, as we have also recommended, that the Food and Drug Administration should pass upon whether a new drug is substantially efficacious for the claims made for it by the manufacturer, and that is the intent of the language in the bill, although it may need some clarification. Your language was "substantial evidence not only that the drug is safe but also that it produces the results claimed." That is exactly what we had in mind in connection with that.

"Mr. BEESLEY. Mr. Chairman, I think we agree in the principle involved. The precise language of the statute is very important, bearing, of course, upon the interpretation that will be given to the statute, and the points which we have made here we think further clarify the statute and are exceedingly important to the way in which it will be administered.

"Senator KEFAUVER. I would certainly accept, as far as I am concerned, your further statement on page 10:

"'Thus if a number of tests by competent clinicians show that in well-conducted clinical trials a drug produced the claimed effect on their patients, the drug would not be barred simply because other tests did not produce the identical results with different patients,' the key words are "well-conducted clinical trials by competent clinicians." I agree with that.

"Mr. BEESLEY. Mr. Chairman, the key words here from our point of view are "substantial evidence." What do we mean by efficacy? What do we mean by effectiveness of a drug? And that is the thought, the new thought, that we are producing there, which, may I submit, is exceedingly important.

"Senator KEFAUVER. Substantial evidence is required in most Government procedures and that is inherent in what we have in mind with the bills." S. Rep. No. 1744, 87th Cong. 2d. Sess., pp. 57-58.

After further consideration, on August 21, 1962, the Senate Committee on the Judiciary issued a second part to its earlier report. At that time, the Senate bill was further amended to include the effectiveness test, including the definition of "substantial evidence" that was ultimately enacted into law. The August 21, 1962, Senate Report further elaborated what was meant by "substantial evidence."

"The proposed committee amendment clarifies and strengthens the previously reported bill by restating and carefully defining the quality and quantum of evidence which the Secretary must find to exist as a basis for clearance of the drug or for withdrawal of a previously approved new-drug application. In the course of committee deliberations a distinction evolved, in this connection, between two tests—the 'proponderant evidence' tests and the 'substantial evidence' test as now specifically defined. Under the former a claim would not be accepted under the new-drug section unless it represented the preponderant view of experts qualified by training and experience in the subject that the claim was supported. The committee recognizes that in the difficult area of drug testing and evaluation there will frequently, if not usually, be a difference of responsible opinion. The committee feels that the existence of such a difference should not result in disapproval of a claim of effectiveness if it is supported by substantial evidence defined in the manner set forth below and evaluated by the Secretary in the light of all the information available to him at the time.

"As the result of subsequent study, a definition of 'substantial evidence' has now been added to the bill concerning what would constitute such evidence. The amendment provides that 'substantial evidence' means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof. That is to say, a claim could be rejected if it were found (a) have the investigations were not 'adequate'; (b) that they were not 'well controlled'; (c) that they had been conducted by experts not qualified to evaluate the effectiveness of the drug for which the application is made; or (d) that the conclusions drawn by such experts could not fairly and

responsibly be derived from their investigations." S. Rep. No. 1744, Part 2, 87th Cong., 2d Sess. p. 6.

The Report of the House Committee on Interstate and Foreign Commerce<sup>1</sup> and the Conference Report<sup>2</sup> do not elaborate further on the substantial evidence concept.

The legislative history could not be more clear in establishing that Congress understood the wide range of opinion that exists in the medical profession as to the effectiveness of any particular drug. Thus, Congress provided a definition of substantial evidence which allows the Secretary to find that a drug's effectiveness is supported by substantial evidence even if that evidence is, in volume, outweighed by opposing views.

#### "ADEQUATE AND WELL-CONTROLLED INVESTIGATIONS"

The issue of the manner in which an applicant should assemble evidence necessary to constitute "substantial evidence" was not directly in question during the hearings. The issue, however, was mentioned in debate as a necessary adjunct to the question of how much evidence would be substantial.

The Senate Judiciary Committee, in its second report, recognized that:

"[I]n the difficult area of *drug testing* and evaluation there will frequently, if not usually, be a difference of responsible opinion. The committee feels that the existence of such a difference should not result in disapproval of a claim of effectiveness if it is supported by substantial evidence defined in the manner set forth below and evaluated by the Secretary in the light of all the information available to him at the time." S. Rep. No. 1744, Part 2, 87th Cong., 2d Sess. p. 6 (emphasis added).

In the vast number of pages which the Senate hearings consume, there is only scant reference to the question of the correct methodology for testing drugs. The absence of long debate on this subject is probably best explained by Secretary Ribicoff's observation that the amendments did not "contemplate any basic changes in the established pattern of testing the effectiveness of drugs."

"Secretary RIBICOFF. Let me make it absolutely clear that we are not dealing here with what some have called 'relative efficacy.' The claim has been made before this subcommittee that the proposed amendment would enable us 'to decide the relative or comparative efficacy of a new drug in terms of drugs already on the market,' or allow us to refuse clearance for a new drug merely because, in the Food and Drug Administration's opinion, it is 'not the most efficacious drug for the purpose intended or was not as efficacious as one might ideally wish.'

"The bill furnishes no basis for such apprehensions. The proposed amendments would merely require a showing that the new drug described in the application is safe for use and is effective in use, under conditions prescribed recommended, or suggested in the labeling thereof. This would not require a showing of relatively greater efficacy than that of other drugs. It would merely require that a drug claimed to be effective for a particular purpose has been demonstrated by sound scientific procedures to be effective for that purpose. In short, it must live up to the claims made for it.

"It should also be pointed out that this proposal does not contemplate any basic change in the established pattern of testing the effectiveness of drugs. . . ." Testimony of Secretary Ribicoff before Senate Subcommittee on Antitrust and Monopoly, September 13, 1961, pp. 2585-2586 (emphasis added).

The subject itself is extremely complicated, as the testimony of Dr. David P. Barr illustrated:

"Every one who has tried to test drugs knows how extremely difficult it is to determine whether a drug is or is not effective, and the establishment of its effectiveness requires extensive facilities and team efforts which may require joint services of many participants, physicians, certainly, and pharmacologists, and others." Testimony before Senate Subcommittee on Antitrust and Monopoly, July 19, 1961, p. 259.

That differences of opinion among responsible clinicians as to effectiveness and testing occur frequently was amply demonstrated in the course of the legislative history.

"The committee recognized that legitimate difference of opinion may exist among responsible clinicians with respect to the effectiveness of a particular

<sup>1</sup> H.R. Rep. No. 2464, 87th Cong., 2d Sess.

<sup>2</sup> H.R. Rep. No. 2526, 87th Cong., 2d Sess.

new drug. Experience has shown that a majority of so-called experts has often been wrong in initially condemning a new drug, just as new inventions in other fields are usually regarded with skepticism and often with hostility. The new ground for rejection of a new drug application is therefore expressed in terms of 'a lack of substantial evidence,' evaluated on the basis of all the information before him, that the drug will have the effect claimed for it. The term 'substantial evidence' is defined in terms of the kind and quality of the investigations that must support the claims." Statement by Senator Eastland, 108 Cong. Rec. 16304 (August 23, 1962).

"In the entire realm of medical science nothing is more difficult and more subject to honest differences of competent opinion than the determination of the therapeutic merits of drugs in human beings. Experts have sharply opposed views concerning the proper treatment of many common diseases, and each school of thought has strong champions. Many highly qualified physicians are convinced of the value of corticosteroid drugs in relieving rheumatoid arthritis; there are others who prefer aspirin; still others are proponents of a variety of other treatments." Testimony of Eugene N. Beesley before Senate Subcommittee on Antitrust and Monopoly, December 7, 1961, p. 1998.

"Mr. BEESLEY. . . . By 'substantial' evidence we mean less than preponderant, or conclusive, evidence.

"We mean that, where a reasonable number of clinicians have conducted tests which show that a drug has the claimed effects, FDA should permit the drug to be marketed even though other tests by other clinicians do not show the same effects. This is a case of difference of medical opinions, which, as Dr. Hussey had said, should not be resolved by the fiat of any authoritarian body but by each physician in his own practice.

"Senator KEFAUVER. All right.

"Then we seem to be pretty well agreed all the way around, sir." *Id.*, at p. 2012.

Only at a few points in the hearings was there focus upon "controlled" investigations. When Dr. Charles May, Professor of Pediatrics at New York University, testified, the concept of a controlled examination was used to distinguish the facilities available to the individual physician. See Hearings before the Subcommittee on Antitrust and Monopoly, July 18, 1961, p. 204.

The same distinction was emphasized by the testimony of Dr. Louis Goodman, Professor of Pharmacology at the University of Utah. See *Id.*, at pp. 217, 243.

The one witness before the Senate hearings who stated that he had "often testified to the importance of double-blind controlled trials in clinical research" insisted that his statements did not constitute a demand for such trials on all new drugs. The witness, Dr. Louis Lasagna, asserted that :

"The emphasis should be on scientifically acceptable evidence, of whatever quality and quantity required to give a reliable answer to the questions posed concerning the drug's effects." Hearings before the Senate Subcommittee on Antitrust and Monopoly, July 19, 1961, pp. 282-283.

In discussing the subject of phraseology, Dr. Lasagna concisely stated a view which permeated the hearings: "I would hope that if such a bill were passed, that there would be every opportunity for a flexibility of interpretation." *Id.*, at p. 288.

The legislative history also includes a statement by Dr. I. S. Ravdin introduced into the hearings before the House Committee on Interstate and Foreign Commerce. The statement was signed by a large number of doctors from all parts of the country, including Drs. Michael E. DeBakey and Paul Dudley White. The statement made the following points :

"(1) Medicine is in part an uncertain science. There is at the present time no precise method for determining absolute efficacy or effectiveness. Such a determination must frequently be based upon medical opinion, and medical opinion is not always unanimous.

"(2) Physicians very often have differing opinions about the usefulness of an agent in treating a particular disease. Many eminent physicians, for example, favor the use of the corticosteroids in the treatment of rheumatoid arthritis, but others believe that the corticosteroids are not the drug of choice for this purpose.

"Under such circumstances, it is difficult, if not impossible, to determine the exact effectiveness of the corticosteroids in treating rheumatoid arthritis. . . ." Hearings before House Committee on Interstate and Foreign Commerce, August 20, 1962, p. 207.

Perhaps the most complete discussion of the problems involved in the working of the substantial evidence standard and the methodology of investigating drugs

was by Dr. Theodore Klumpp, the President of Winthrop Laboratories, before the House Committee on Interstate and Foreign Commerce.

Dr. Klumpp testified that:

"Despite advances in scientific techniques, therapeutic representations and claims remain essentially matters of opinion. Different schools of thought with respect to the proper treatment of various diseases are prevalent and sometimes completely contradictory. Not infrequently, it takes years and sometimes decades of widespread clinical experience to evaluate the true or relative merit of a drug in given conditions. From such long experience, a medical consensus generally emerges, but even then some qualified physicians refuse to go along with their colleagues. . . ."

"At the present time, there are sharply opposed views among experts concerning the proper treatment of many common diseases. Rheumatoid arthritis is such a condition. There are highly qualified physicians who favor the use of corticosteroid drugs. There are others who feel that the employment of the corticosteroids does more harm than good and that the only meritorious drug is aspirin. Still others are proponents of, respectively, Butazolidin, gold salts, and antimalarial drugs such as quinacrine, chloroquine, and hydroxychloroquine. The use of pyramidon, or large doses of vitamin D, still has adherents, and particularly among clinicians in foreign countries. The reaction of experts to any new drug offered for the treatment of rheumatoid arthritis will inevitably be conditioned by the school of thought to which they happen to adhere. By whose advice is FDA to be guided in the evaluation of a new drug for this condition?"

[Dr. Klumpp then considered similar problems with drugs for epilepsy, mucous colitis, and the common cold.]

The above specific illustrations are only a few of the many that can be cited to show that—

(a) The determination of the effectiveness of a drug is always difficult and sometimes cannot be achieved except by the test of time and widespread use.

(b) Therapeutic representations are essentially matters of opinion.

(c) Differing schools of thought frequently exist concerning therapeutic issues, and the school which favors one theory as to the nature and treatment of disease tends to be skeptical of the drugs advocated in opposing schools. Moreover, medical opinions as to effectiveness of a particular drug can differ widely among equally qualified physicians because of basic differences in opinion relating almost entirely to questions of diagnosis and preferred method of treatment, as well as differences as to the comparative efficacy of one member of a class of drugs in relation to others or the mode of action of a particular drug in the complex body mechanism. Hearings at pages 232-235.

#### CONCLUSIONS

The legislative history of the 1962 amendments establishes quite clearly that Congress did not intend "substantial evidence" to mean a preponderance of evidence. Nor did Congress expect the medical profession to arrive at single conclusions about drugs and treatments. Rather than enacting standards which would require exact proof and which could leave no room for minority opinions, Congress explicitly favored concepts of flexibility which could accommodate the range of responsible professional opinions.

Had Congress disagreed with Secretary Ribicoff's view that the amendments would not change the established pattern of testing drugs, there would have been more discussion on the subject of the methodology of drug testing. But Congress did not take issue with the Secretary's assessment of the law, and the legislative history shows that Congress intended to maintain flexibility in the area of drug testing, just as it so intended with the concept of substantial evidence.

The substantial evidence standard itself, as enacted, requires a comparable openness with regard to differing opinions in the area of what constitutes adequate and well-controlled investigations. It may well be that certain drugs for some kinds of diseases are better investigated with some techniques than with others. A substantial difference of opinion might exist about which methods of testing should be applied in different circumstances. It would be wholly inconsistent with the clear and unambiguous intent of Congress with respect to the substantial evidence standard to conclude that only certain kinds of tests could produce such evidence when there is a body, however small, of reliable professional opinion to the contrary. An "adequate" test for one situation might be inadequate in others; the kinds of controls possible in one instance might be impossible of achievement, or less meaningful, in another; and even the qualifications of

persons performing clinical investigations can be matters for honest differences of opinion.

The substantial evidence standard itself concedes that room must be left open for well-founded differences of opinion. That standard would become rigid, and precisely what Congress expressly intended to avoid, if one point of view about the proper methods of testing drugs were allowed to dominate and exclude other points of view. As long as a sound professional difference of opinion about the merits of different methods of drug investigation exists with regard to particular drugs, it is clear from the legislative history of the 1962 amendments that a single view, especially one which seeks exact answers in inexact areas, cannot properly be considered the "only scientifically sound method for drug testing."

Senator NELSON. I have a letter that I received from the Department of Health, Education, and Welfare, signed by Theodore Cron. Mr. Cutler has a copy of this letter as does the press. I will ask to have it put into the record at the appropriate place after yesterday's testimony.

Mr. GADSDEN. I might ask, are we going to revert for a moment to—you are putting Mr. Cron's letter into the record? I am asking the privilege now or later of talking on the substance of what is going in the record.

Senator NELSON. All right. The appropriate place for this, I would assume, is after yesterday's testimony.<sup>1</sup> If you would like to comment on it now, I will ask that your comments be placed in the record after this letter.

Mr. GADSDEN. Yes, sir.

Senator NELSON. Or, if you wish to submit something later that you will prepare, you may do so.

Mr. GADSDEN. I would like to comment here, and then we can decide into what degree of detail you want to go, sir.

First, I think it is important to record that at the time of the release of indomethacin by the Food and Drug Administration, I, as the chief executive officer of the company, issued an order that under no circumstances were we to seek any lay publicity in connection with it—its benefits, or anything else. I assume, lest we have any confusion here, that you are alluding to the same Mr. Cron letter which I have in front of me?

Senator NELSON. It has no date.

Mr. GADSDEN. The first sentence begins "You will recall that Dr. McCleery."

Senator NELSON. Yes, that was delivered here this morning at about 10:45. I am referring to that letter.

Mr. GADSDEN. I would like to make a statement on that, sir.

A free-lance writer and TV fellow, Mr. Goldman, called our director of public relations, Mr. Fletcher. Mr. Goldman said his wife had suffered from tennis elbow and had been unable to play and that her doctor prescribed "Indocin" and it worked miraculously. He had checked around and found a lot of doctors who were using it effectively, and said he was going to write a story about it. He was upset with the company, namely Merck & Co., for not telling people about the drug, and he asked the company for background materials, which we sent him.

He was told that tennis elbow is not an approved claim, and he was also told why the company had elected not to publicize the drug.

<sup>1</sup> See p. 3294, supra.

Several weeks ensued. Mr. Goldman did not visit the company or talk with anyone in the company about the drug or the story he was writing. Then he called Mr. Fletcher again, said his story was essentially finished, said he had a lot of anecdotes to liven it up, and asked if the company could provide additional anecdotal material to personalize it still further.

Mr. Fletcher supplied him with four or five letters from our files, deleting the names of the correspondents. They dealt with approved claims.

There is, as I understand it—and I will check it if this is material—an attribution of a nonapproved claim in the article. This was not among the cases supplied to him by Merck & Co.

Senator NELSON. What is an approved claim?

Mr. GADSDEN. The four that were enumerated earlier, sir, which have to do with various aspects of arthritis.

Senator NELSON. What is an approved claim?

Mr. GADSDEN. When we make a submission to Food and Drug, as we discussed earlier, we request—let us call them indications. Perhaps that is a more precise term than "claims," meaning for what disease conditions use of the drug is indicated. The FDA must approve these indications. The thrust of the criticism is that we were seeking through lay publicity to publicize and popularize the use of this drug for conditions—indications—which had not been approved.

Senator NELSON. I see.

Mr. GADSDEN. I will continue, sir, if I may.

We were altogether unprepared for the appearance of this Pageant article, with the name of the drug as the title of the article, and a subtitle that enumerated its value for a number of conditions for which we had no claim.

Senator NELSON. That will go into the record immediately following this letter so that they will both appear in the appropriate place in the record.

Mr. GADSDEN. Counsel reminds me, sir, that contrary to the statement that is contained in the letter which has gone into the record, Mr. Fletcher did not see the article until after it was printed.

Mr. CUTLER. Also, Mr. Chairman, the article itself, as I understand it, refers to one letter which the author says he got from Merck relating to the use of the drug for an unapproved claim. No such letter was furnished by Merck.

Senator NELSON. Thank you.

Again, thank you, Doctor.

Dr. LAWASON. Before introducing the two outside witnesses, Dr. Calabro and Dr. Smyth, the two physicians, who will summarize their views and the views of physicians who are treating patients with arthritic disorders, I have with me an even broader representation of medical opinion concerning the values and limitations of indomethacin that we hereby submit to you with the request that it be made part of the official record.

Senator NELSON. Would you identify what it is?

Mr. CUTLER. It is this green folder which you should have up there, Senator Nelson.

Dr. LAWASON. This exhibit, Mr. Chairman, consists of letters and telegrams from distinguished rheumatologists and experienced physi-

cians across this country and around the world. I want to tell you how they came to us.

When we learned that this committee was planning to hold hearings on indomethacin, we asked a number of investigators who we knew had worked with indomethacin to give us, so we could give to you, their frank appraisal of the drug. Their names and positions and reputations speak for themselves, and also bespeak the fact they would support no drug and no drug company if the facts did not warrant support. We are submitting here every communication we have received, exactly as it came to us. When the committee examines this documentation, it will find it represents the full range of medical and scientific opinion. Some investigators have found indomethacin very useful, some have found it useful in some conditions and not in others; some have found it only marginally useful.

This sample of professional judgment on the part of physicians using indomethacin in their practice reinforces our conviction that when properly used, it is a safe and effective drug that benefits hundreds of thousands of patients. I would like to ask your permission that these letters and telegrams be put in the record.

Senator NELSON. You want it in the record at this point?

Dr. LAWRAZON. Yes, sir.

Senator NELSON. They will be put in the record at this point.  
(The documents referred to follow :)

RECEIVED FROM DR. F. DUDLEY HART, WESTMINISTER HOSPITAL, ENGLAND

In the light of your extensive experience in the management of diseases for which indomethacin is indicated—

(1) Do you consider that the introduction of indomethacin has contributed to the management of your patients? Yes.

(2) Do you find that indomethacin enables you to obtain results in some of your patients that were difficult to obtain prior to its introduction?

(3) If so, can you define those areas in which the drug has been most helpful?

(a) In acute gout, I would rate it the drug of first choice. Good as are the pyrazoles, we find their action slightly slower, and in this disease a quick result is all-important. Our order of preference is indomethacin first, phenylbutazone and oxyphenbutazone second and colchicine third.

(b) In ankylosing spondylitis, although aspirin is suitable for the mild cases, taken as required, if larger regular anti-inflammatory dosage is necessary, few men doing active work, as are 80% of those attending our clinic, can (or will) take such dosage, and much prefer indomethacin or the pyrazoles. We consider the last two equally effective, but the real but rare danger of blood dyscrasias with the pyrazoles now leads us to try indomethacin first, and only proceed to the pyrazoles if results are unsatisfactory. We try flufenamic acid next, as we find it less effective.

(c) We find indomethacin helpful in half our cases of rheumatoid arthritis, and consider its anti-inflammatory action less than that of the corticosteroids or corticotrophin, but greater than that of the other non-steroidal anti-inflammatory agents. The trial and error method which is necessary in the treatment of rheumatoid arthritis must leave some choice to the patient, who finds large numbers of aspirin tablets tedious to take in many instances, and they will not, and do not, take them. We start with aspirin and only go on to other drugs if therapeutic results are poor to toxic effects troublesome. A number of patients with rheumatoid arthritis prefer indomethacin and do better on it than any other agent. Because of the unwanted endocrine effects, we use corticosteroids only in small dosage in selected patients.

(d) We find indomethacin a useful drug in Reiter's disease.

(e) In osteoarthritis of cervical spine and hip, we find indomethacin a useful substitute for the pyrazoles, which, though very useful, have the danger of causing blood dyscrasias, though rarely. This is the main reason for preferring indomethacin to the pyrazoles, for in most other respects the drugs are equally effective in the same group of disorders.

LOVELACE CLINIC,  
Albuquerque, N. Mex., April 19, 1968.

**Dr. MAX TISHLER,**

*Merck Research Laboratories, Merck & Co., Inc., Rahway, N.J.*

DEAR DR. TISHLER: I understand that there are to be hearings very soon in Washington regarding the efficacy of certain drugs which have been marketed in recent years. Among these I understand that Indocin is one to be considered. I should like to state that I have used Indocin since it first became available, even before it was marketed and that in selected instances I feel that this is a very notably effective and safe drug. I feel that its indiscriminate use, just as the indiscriminate use of any medication without adequate reason, is unwarranted. However, in my opinion, it is the drug of choice in such cases as rheumatoid spondylitis and degenerative arthritis involving the spine and hips especially. Its use in gout is according to literature, very definitely an appropriate measure and with less drastic effects than some of the other medications that are available for treatment for this acutely painful process. My own experience is no extensive enough with this particular problem to warrant comment.

I feel that much of the "poor publicity" which has surrounded Indocin is a result of its indiscriminate use in many instances where it has not been warranted. In my own experience, it is not nearly as effective in peripheral rheumatoid arthritis as it is in the other instances mentioned above. So far as its toxicity is concerned, I feel that the serious problem has to do with gastrointestinal irritability, the symptoms of which are quite readily apparent and if both doctor and patient are aware of this problem, serious trouble can be easily avoided. I have not yet run into any other significant toxic reactions to this drug that would indicate any serious effects on health.

I feel that from the standpoint of all available information in the literature that merits consideration there is adequate information regarding this drug, that further investigational procedures would be a waste of time and a waste of money and would deprive certain patients from the use of a drug that has very definite value to them.

Very truly yours,

C. M. KEMPER, M.D.

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RICHARD W. PAYNE, M.D.

*Oklahoma City, Okla., April 20, 1968.*

DEAR DR. TISHLER: I hear that there is some movement afoot to curtail the use of Indocin. If this news is correct, I would like to put myself on record as finding Indocin indispensable in my practice of rheumatology. The agent has a relatively low order of serious side effects and is of undoubted value in the practical long-term management of many patients with various types of arthritis.

While there are double-blind studies which question the efficacy of Indocin—I am equally prone to question the validity of such studies that I have seen, including my own.

After 6 yrs. experience with Indocin I have no doubt that it is a valuable therapeutic agent in a group of diseases notoriously difficult to treat. That we don't know exactly how it produces its beneficial effects is no fault of the drug.

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MEMORIAL HOSPITAL,  
*Charleston, W. Va., April 20, 1968.*

**MAX TISHLER, Ph. D.,**

*Merck Research Laboratory, Merck & Co., Inc., Rahway, N.J.*

DEAR DR. TISHLER: It is my understanding that you and your associates will be appearing before a Congressional Hearing very shortly to engage in dialogue and data gathering regarding indomethacin and its clinical benefits in the treatment of particularly rheumatoid arthritis, as well as the double blind method of drug evaluation. I thought that you might, therefore, be interested in some of my personal conclusions regarding these two issues based upon my experience with double blind study using Indocin and placebo, as well as experience with indomethacin prescribed to rheumatoid arthritis patients these past three years.

Regarding the double blind method in evaluating drugs for rheumatoid arthritis, I think there is universal agreement that this is still not the answer to evaluation of drugs for this disease, but it is the best we have available at this time. In the first place, rheumatoid arthritis is so variable from day-to-day, week-to-week, and month-to-month that any change short of virtual remission of the disease must be submitted to the mathematical probability wherein the results

are trends and not conclusive evidence. Secondly, in the measurement of activity of disease in rheumatoid arthritis there is also apparent universal agreement that there is still no satisfactory means of doing this. Lansbury's criteria, measurement of the inflammation of the joints, the swelling, mobility, general well-being of the patient, etc., all have a certain subjective element and a wide standard deviation. Typical example is the objective measurement of the knuckle circumference or the knee circumference. This requires no judgment on the part of the patient; however, in order to arrive at a probable accurate mathematical figure, the measurement of his joint must be done by the same person at each observation and several times each observation, even then, the other variables of swelling of the extremities due to causes not related to rheumatic disease are never determinable. This same problem can be applied to all the other objectives and are certainly applicable to the subjective measurements for rheumatic activity. But, I repeat, that this is all that we have at this time and I eagerly search the literature and discuss with my colleagues any developments in this area.

Regarding Indocin and its effectiveness—Indocin is presented as an anti-inflammatory drug and is ranked with aspirin, phenylbutazone, adrenocortical steroids and lesser anti-inflammatory agents. Whether antimalarials are actual anti-inflammatory in the sense of these drugs has never been really determined. I think organic gold salts are not considered primarily anti-inflammatory. Of all these drugs, gold in my impression and the impression of the literature has been the one that has stood the test of time and double blind study as being *probably* causative in the induction of remission in rheumatoid arthritis. Thus, indomethacin, an anti-inflammatory drug, cannot offer the promise of remission, but rather a reduction in pain and swelling, and perhaps a delay of the destructive consequences of sustained synovitis. This latter has not been proven even for aspirin, and definitely has not been proven for steroids. Steroids may prevent ankylosis and result in a mobile destroyed joint, which is more amenable to surgical therapy. Perhaps a good and consistent use of other anti-inflammatory drugs like Indocin would do the same and have this benefit.

My colleagues in West Virginia, realizing my interest in rheumatology and my experience with the use of Indomethacin have asked me—what do I think of the drug? I tell them at this point that indomethacin is a definite anti-inflammatory drug and it is as good as the other anti-inflammatory agents mentioned above. The next question is—why should I use it above the others? I refer them to the serious side effects of phenylbutazone and adrenal steroids, which brings us down to the discussion as to whether it should be used in addition to or rather than salicylates; and this apparently is the issue that has appeared in the literature. I then say that effective salicylate therapy demands the continuous administration of sub-tinnitus dosage of the drug and this means that the patient must be experiencing from time to time tinnitus as well as diaphoresis, cerebral symptoms, etc., and requires a dosage from 12 to 18 tablets a day. I submit that the problem of getting the patient to take that number of tablets every day for years is in some cases insurmountable; but the same can be accomplished with approximately 6 capsules of Indocin a day. This is then the current pragmatic feeling on my part regarding the use of indomethacin in the spring of 1968. We are currently in the process of retrospective analysis of patients treated 18 months or more with all the above drugs, singly or in clusters, including indomethacin. These are in the hands of our biostatistician and will be made available when completed.

Very truly yours,

DANIEL HAMATY, M.D., F. A. C. P.

MEDICAL COLLEGE OF VIRGINIA,  
Richmond, Va., April 22, 1968.

MAX TISHLER, Ph. D.,  
Merck & Co., Inc.,  
Rahway, N.J.

DEAR DR. TISHLER: It has recently come to our attention that in the near future inquiries will be held concerning the efficacy of Indocin (Indomethacin).

Indocin is no panacea in the treatment of rheumatoid arthritis but it definitely has a place in its treatment and in the treatment of other rheumatic disease such as gout, osteoarthritis, and ankylosing spondylitis.

The management of rheumatic arthritis involves a treatment program of some complexity. No rigid set plan of drug therapy should be followed. A program

which proves beneficial in one patient may not in another. If one medication proved effective in all patients, there would be no need for the long list of available medications. If one method of approach does not prove effective, another should be pursued.

Aspirin or some other salicylate preparation should be given initially in essentially all cases of rheumatoid arthritis. If after several weeks no clinical improvement is experienced, another agent should be added. We frequently use Indocin as the second agent and will continue to use it in this capacity. Also, we have found the drug to be helpful in selected cases of osteoarthritis, acute gouty arthritis, and ankylosing spondylitis.

Sincerely,

DUNCAN S. OWEN, Jr., M.D.,

*Assistant Professor of Medicine, Division of Connective Tissue Disease.*

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MEDICAL COLLEGE OF VIRGINIA,  
Richmond, Va., April 22, 1968.

Dr. MAX TISHLER,  
*Merck Research Laboratories,*  
*Merck & Co., Inc.,*  
*Rahway, N.J.*

DEAR DR. TISHLER: It has come to my attention that there will be a Congressional Hearing regarding the efficacy of Indomethacin (Indocin) in the treatment of rheumatoid arthritis and related rheumatic disorders. My personal feeling about this drug is that it has a definite place in the treatment of rheumatoid arthritis and in certain cases has a very beneficial result. There have been certain side effects which prohibit its use, but none have been of a serious nature in my experience.

Many investigators state that "double blind" and "double blind crossover" studies are the only ways to properly evaluate the effect of a drug. It is my feeling this does not always hold true in the case of rheumatoid arthritis. Patients with rheumatoid arthritis will vary as to their physical abilities throughout the period of day's time and the natural history of rheumatoid arthritis with remissions and exacerbations are two factors which make the double blind study difficult to evaluate in this disease. If there were a more realistic method of evaluating efficacy or lack of same in the rheumatic diseases, this would be most helpful.

Yours sincerely,

ROBERT IRBY, M.D.,

*Associate Professor of Medicine,*  
*Medical College of Virginia, Richmond, Va.*

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HOLBROOK-HILL MEDICAL GROUP,  
Tucson, Ariz., April 22, 1968.

MAX TISHLER, Ph. D.,  
*Merck Research Laboratory,*  
*Merck & Co., Inc.,*  
*Rahway, N.J.*

DEAR DR. TISHLER: Dr. Richard Smith telephoned me this morning asking me to write to you regarding my impressions about Indocin and my thoughts about double blind studies for evaluation of agents for treatment of rheumatoid arthritis.

First, in regard to Indocin, our group did conduct a clinical trial to study efficacy and toxicity before Indocin was marketed. These studies were limited primarily to rheumatoid arthritis and unfortunately, did not show consistent results. There were a few patients who felt that Indocin gave them much more relief than other analgesics or anti-inflammatory compounds but we did not feel that the drug altered the course of the disease. We continue to use Indocin in a limited number of patients where they feel it has been of help to them. Unfortunately, a number of our patients were unable to tolerate the drug.

In regards to double blind studies with rheumatoid arthritis, it has been most difficult in our experience, to get a true assessment as to its efficacy. This is probably due to the fact that we have such a wide variation, not only in disease activity and extent, but also in patient variability in age, personality, motivation,

etc. We are now in the process of trying to improve our methods of evaluation through a system of gross measurements, correlating the subjective with the objective findings.

Trusting this is the information you desire, I am  
Sincerely,

DONALD F. HILL, M.D.

THE UNIVERSITY OF IOWA,  
*Iowa City, Iowa, April 22, 1968.*

Dr. MAX TISHLER,  
*Merck Research Laboratory,*  
*Merck, Sharp & Dohme,*  
*Rahway, N.J.*

DEAR DR. TISHLER: I am enclosing two of the Bulletins that we have written giving our experience with indomethacin.<sup>1</sup> You will notice that the last one was written in 1965.

Since that time we have continued to use indomethacin, particularly in rheumatoid arthritis, and are of the same opinion, namely, that this drug is a safe and effective anti-inflammatory medicament in the management of rheumatoid arthritis. Over the years we have used this drug only in conditions in which we could make a definite diagnosis, and from our past experience knew that it would be effective. These conditions were rheumatoid arthritis, gout, Reiter's disease, and a few cases of degenerative arthritis. We have not prescribed this drug in the conditions that are difficult to accurately diagnose, or in which we are limited only to the patient's response. These include low back pain, fibrositis, painful shoulder, and pains in elderly individuals which are, unfortunately, classified as osteoarthritis.

Most physicians are very impatient and think that an anti-inflammatory drug should relieve or cure a chronic ailment such as rheumatoid arthritis in a short period of time. We have found many patients who were on adequate treatment but still continued to have mild degrees of synovitis. The swelling caused by the synovitis results in pain which is difficult to control. When these people are given indomethacin, in addition to the treatment they are receiving, the synovitis gradually decreases, and improve clinically. This, however, may take several weeks rather than a few days. By the same token when we see a new rheumatoid we usually start them on salicylates and if we cannot hold them with this drug, we usually add indomethacin. A high percentage of the patients that we have do well, but a few continue to show intermittent exacerbations and must be given other drugs as well, including steroids, or gold, etc. If one of our patients has been on steroids, we will add indomethacin in an attempt to reduce the dose of steroids to a safe level. As you know, we believe that rheumatoid arthritics should not receive more than a total of 8 mg. of prednisone, or its equivalent in other steroids, per day. Indomethacin has helped us reduce the steroid dose and prevent many of the side-effects caused by the steroid.

Since 1965, our usual dose of indomethacin is 75 mg. per day. With this dose we see fewer side effects than we reported in the enclosed Bulletin. At times we may give 100 or 125 mg., but cut back as soon as the patient has dizziness, muzziness, or other irrelevant effects. In our hands, indomethacin is a very safe drug.

I was surprised to hear that a Congressional Committee is investigating indomethacin. I suppose this has been started because of the some of the recent reports on the double blind studies. It is in these studies that one finds many of the loosely defined syndromes being treated, as well as rheumatoid arthritis. Most of these studies depend on the patient's own response to the drug given for a short period of time, usually about two weeks. It is difficult to determine the effect of indomethacin in the ill-defined syndromes. Even in rheumatoid arthritis we have seen severe and relentless progression of the disease despite every type of heroic therapy that we try. It is a well known fact that individuals with a high titer of the rheumatoid factor will have progression despite anything that you do. It is not unusual to see an individual with a very high titer have breakdown of the joints in the wrists and fingers, even though they are getting adequate physical therapy, adequate doses of salicylates, steroids, indomethacin, and/or gold. On the other hand, people who have a low titer may have a remission for long periods of time with little or no destruction of joints. In any double blind study, one has both types of patients, and therefore any drug will not work in

<sup>1</sup> Retained in committee files.

some arthritics and will appear to be an excellent drug in others. We are very conscious of this as we try to separate these two groups and select the severe ones as candidates for prophylactic surgery (synovectomy, etc.).

In conclusion, our group at Iowa feel that we could not treat rheumatoid arthritics adequately without indomethacin.

Sincerely yours,

W. D. PAUL, M.D.

PAUL YOUNG, M.D.,  
Asheville, N.C., April 22, 1968.

Dr. MAX TISHLER,  
Merck Research Laboratory,  
Rahway, N.J.

DEAR DR. TISHLER, I have been in the full time practice of rheumatology as a private practitioner since 1958. I believe that I am one of the very few physicians in the country who is in this position of making a full time professional activity out of the treatment of arthritis. Over half of my practice consists of patients with rheumatoid arthritis and I am treating approximately 300 such patients all the time for the last five to ten years.

I have been actively engaged in the evaluation of new drugs for the treatment of arthritis and was doing this in practically all of my patients in the period of 1960 to 1963. I discontinued these endeavors in 1963 because of the enormous amount of paper work which was generated by the law which was passed in 1962 where you had to prove that you were taking the same precautions we had been taking all the time. During the period of 1960 to 1963 I was engaged in the evaluation of 18 different drugs in the treatment of arthritis on some 3000 patient/drug combinations.

I have been quite familiar with the work of the committee on cooperative clinics of the A.R.A. since 1960. It was at my suggestion that the CCC engaged in the study of variability in rheumatoid arthritis in about 1963. I am personally acquainted with well over half of the physicians involved in the CCC studies and I am quite familiar with their drawbacks and limitations.

I am not particularly enthusiastic about the use of Indocin in rheumatoid arthritis because I feel that this has only analgesic and anti-inflammatory effect and prefer to use compounds such as gold and the anti-malarials for the long term treatment of this disease. However it is beyond any reasonable doubt that Indocin does give effective relief of the symptoms of rheumatoid arthritis and in some patients this is the most effective remedy of its type on the market. Probably aspirin would do just as good a job if patients could take 30 aspirin a day, but in my experience most patients cannot take 12 aspirin a day on a regular basis whereas many can take Indocin. It is ridiculous to argue that Indocin is no better than aspirin when many patients cannot take aspirin.

With respect to the recent questions that have been raised by the CCC trials of Indocin, I would like to say that under the circumstances of these trials the types of patients used would not very well demonstrate the effect of Indocin. Due to the nature of the disease, rheumatoid arthritis, Indocin is most effective in patients who have not developed joint deformities and secondary complications of the disease due to anatomical damage. If this study had been confined to patients without deformity and with most of their symptoms being due to the pure inflammatory effects of arthritis there would be in my mind, absolutely no question but that Indocin would have been shown to be an extremely effective drug for relief of inflammatory symptoms due to rheumatoid arthritis.

For physicians who are thoroughly and professionally acquainted with the nature of rheumatoid arthritis it is not necessary to do the "double blind" studies in order to tell whether a drug is effective or not. It certainly is necessary to do this type of study in order to tell whether one drug is more effective than another drug in a *similar* type of patient.

In conclusion, I would like to state that the recent questioning of the value of Indocin in rheumatoid arthritis merely illustrates the ignorance of the people asking the question and the lack of familiarity with the nature of the disease, rheumatoid arthritis, and the proper precautions to be evaluated in judging therapeutic efficacy.

It would be a great disservice to the public at this time to raise any question which could lead to the withdrawal of Indocin for treatment of patients with rheumatoid arthritis. The drugs we have to use in treating rheumatoid arthritis are not as good as we would like to have but there are some patients who desperately need each and every one of them.

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ARTHUR DOBKIN, M.D.  
Akron, Ohio, April 22, 1968.

Dr. MAX TISHLER,  
*Merck Research Laboratories,*  
*Merck & Co., Inc.,*  
*Rahway, N.J.*

DEAR DR. TISHLER: I am one of a few physicians in this metropolitan area who have been interested in and practicing Rheumatology for a number of years. I have used one of your drugs, Indocin, ever since it was released several years ago. In my experience with this drug, I find that it has a useful place in the therapy of arthritis. I fully realize that it has no curative effects, nevertheless, I have found "Indocin" to be beneficial in a selected and limited number of arthritis patients. It has been effective in relieving the symptoms of a number of patients with Rheumatoid Arthritis, Gouty Arthritis, as well as Osteoarthritis and Rheumatoid Spondylitis.

"Indocin", like many other medications now used in Arthritis, none of which are curative, will therefore have a place in the treatment of the Rheumatic Diseases in selected cases—at least until such time as newer and more effective medications are available.

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MAYO CLINIC,  
Rochester, Minn., April 22, 1968.

MAX TISHLER, Ph. D.,  
*President, Merck Sharp & Dohme Research Laboratories,*  
*Rahway, N.J.*

DEAR DR. TISHLER: It is my understanding that a congressional hearing is soon to be held in which the efficacy of indomethacin may be challenged. I do not know the basis for this contest but if the opportunity presents itself, I would be pleased to have you convey my opinion that indomethacin has served a useful function therapeutically. The record clearly shows that it has been adequately tested on an experimental basis prior to its introduction for clinical usage and that widespread clinical trial has indicated an acceptable risk of occasional intolerance on the part of certain patients. It should be noted, however, that all known anti-inflammatory drugs seem to have a tendency to gastrointestinal bleeding but that this does not seem to be an overriding interference to the use of anti-inflammatory drugs in general. As a matter of fact, the public interest would not be served by the elimination of anti-inflammatory drugs.

I feel further that the medical profession has been amply instructed in the proper usage of indomethacin. The challenge to indomethacin on any basis with which I am familiar is in my opinion unwarranted and probably prejudicial.

Sincerely yours,

H. F. POLLEY, M.D.

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VETERANS' ADMINISTRATION CENTER,  
Los Angeles, Calif., April 22, 1968.

Dr. MAX TISHLER,  
*President,*  
*The Merck Foundation,*  
*Merck & Co.,*  
*Rahway, N.J.*

DEAR DR. TISHLER: It is my understanding that there will be a congressional hearing soon to consider, among other things, the current controversy that has been brought forth regarding the antirheumatic efficacy of indomethacin. I would assume that this is somehow related to the results of more recent double-blind evaluations with indomethacin in rheumatoid arthritis (RA).

It is my opinion that while double-blind studies are obviously useful in evaluating new agents, they are also extremely difficult, particularly in such a capricious disease as RA. To this point, I might add that there are few (if any) double-blind trials with other antirheumatic agents that are entirely satisfactory.

Even more appalling are the apparent expectations of many investigators conducting short-term studies in RA that indomethacin would provide objective functional improvement. This is a clinical misconception since all antirheumatic agents are at best palliative. By providing effective relief of joint pain and inflammation, drugs allow patients to undertake therapeutic exercise and other supportive measures. These provide objective improvement. Yet, such measures receive scant mention and do not appear to be an integral part of the reported double-blind studies of indomethacin in RA.

In spite of these controlled trials, many physicians have the impression that indomethacin benefits certain patients with RA. As Healey has recently pointed out in the Bulletin of the Rheumatic Diseases (18, 483, 1967), there may be a sub-group of patients with RA that are controlled by indomethacin, a finding that would not be evident when such patients are included in a general drug trial. To my knowledge, this hypothesis has not been tested.

The result of our long-term evaluation of indomethacin in ankylosing spondylitis (AS), a form of rheumatoid disease affecting young men, has recently appeared in the journal Arthritis and Rheumatism (11, 56, 1968).

In this trial of indomethacin averaging 33 months in 28 AS patients who received an average daily dosage of 100 mg., the response to the drug was good in 21 patients, fair in 5 and poor in 2. Of the 28 patients, 21 improved to ARA functional class I. Before the use of indomethacin, only one of the 28 was so rated. Joint symptoms followed temporary withdrawal of the drug in all but four of the 28 patients. These symptoms were promptly relieved when indomethacin was again taken by the patients.

Clearly, our report parallels the experience of others, such as Bilka, Hart, Kass, Pohl, Rothermich and De Seze, that indomethacin is an essentially safe and effective drug in suppressing the articular manifestations of AS.

I sincerely hope, despite the current controversy and confusion, that investigative pursuits of indomethacin will continue. Only then can we more fully understand the role of this extremely useful and valuable antirheumatic agent. Best wishes.

Very truly yours,

JOHN J. CALABRO, M.D.  
Chief, Rheumatology Section, Wadsworth Hospital.

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ST. LOUIS UNIVERSITY,  
SCHOOL OF MEDICINE,  
St. Louis, Mo., April 22, 1968.

MAX TISHLER, Ph. D.  
Merck Research Laboratories,  
Merck & Co., Inc.  
Rahway, N.J.

DEAR DR. TISHLER: I understand that indocin is under Federal scrutiny in regard to its effectiveness in rheumatoid arthritis. Since I am presently performing a double blind study with this drug in the treatment of rheumatoid arthritis, I would like to offer the following comments.

The therapy of rheumatoid arthritis, as you know, is very difficult. Fortunately, we have many drugs available today which help the practicing physician control this crippling illness in most patients. Many times we find it necessary to use several medications in the same individual because of a lack of any specific drug which will perform to the degree of satisfaction we desire. Some of these drugs are rather toxic, thereby obviating their routine usefulness. By combining drugs like indocin with some of the more toxic medications, we are thus able to effectively use some of the latter preparations in smaller dosages and, consequently, avoid some of their complications. This would be particularly true of the steroids, the "cortisone-like" drugs. Also, when used alone, indocin may offer significant relief so that the addition of other antiflammatory drugs may not be necessary.

Despite the fact that indocin's value in rheumatoid arthritis has been questioned recently, it is my opinion that this medication certainly has a place in the therapy of rheumatoid arthritis. I do not administer indocin as a drug of first choice; however, I do believe it offers a significant advantage to approximately fifty percent of rheumatoid patients.

Evaluation of any drug for the treatment of rheumatoid arthritis is extremely difficult. Double blind studies, such as those being performed at the present time, seem to be the appropriate method of determining a drug's effectiveness. If n

sufficient number of patients are studied, satisfactory answers should result from such studies. The difficulty in evaluating a drug for the treatment of rheumatoid arthritis arises because of the many patients who will improve with placebo therapy. Also, objective manifestations of improvement are frequently very difficult to measure with any degree of accuracy in rheumatoid arthritis. If there is doubt about indocin in the treatment of rheumatoid arthritis, I believe that double blind studies should give the most reliable information in its efficacy.

Sincerely yours,

JACK ZUCKNER, M.D.,  
*Associate Clinical Professor,  
Director, Section of Arthritis.*

PITTSBURGH, PA., April 22, 1968.

MAX TISHLER, M.D.,  
*Merck Research Laboratory,  
Merck & Co., Inc.,  
Rahway, N.J.*

DEAR DR. TISHLER: This is in reply to an inquiry from Dr. Richard Smith concerning our findings and results in the clinical therapeutic use of Indomethacin (Indocin).

Although we have not employed double-blind controls, our extensive experience in the management of patients with rheumatic disease has indicated to us over the years that through close clinical observation of our patients under treatment we have generally arrived at conclusions concerning clinical effectiveness of therapeutic agents which closely approximated those reported in controlled therapeutic trials.

Our own experience over an extended period of time has indicated a significant degree of effectiveness of Indocin as an anti-inflammatory agent in a considerable proportion of patients with rheumatoid spondylitis, gouty arthritis, osteoarthritis of the hip, and some patients with rheumatoid arthritis.

The incidence and character of side effects have likewise corresponded with those described in the literature.

In conclusion, we feel that Indocin in appropriate clinical situations offers a useful addition to our therapeutic armamentarium.

Sincerely yours,

H. M. MARGOLIS, M. D.  
JAMES H. BARR, JR., M. D.  
BERTRAND L. STOLZER, M. D.  
CARL H. EISENBEIS, JR., M. D.  
BURTON H. POLLOCK, M. D.

UNIVERSITY OF MIAMI,  
*Miami, Fla., April 22, 1968.*

Dr. MAX TISHLER,  
*Merck Research Institute,  
Merck & Co., Inc.  
Rahway, N.J.*

DEAR DR. TISHLER: I understand that your company is under investigation by the Subcommittee on Monopoly, chaired by Senator Nelson, in reference to the drug, Indocin.

In our University Clinic we use Indocin, quite effectively, for pain relief in the milder cases of rheumatoid arthritis. Certain patients, particularly males, have better response to Indocin with less side effects than when given large doses of aspirin or mild narcotics. Business men are able to get pain relief without drowsiness. We use Indocin for lowering the dosage of Prednisone. Thus, I think, Indocin is a useful adjunct in the treatment of various arthritics.

Sincerely yours,

DAVID S. HOWELL, M.D.,  
*Professor of Medicine,  
Director, Arthritis Division.*

LOS ANGELES, CALIF., April 22, 1968.

Dr. MAX TISHLER,  
Merck Research Laboratories,  
Merck & Co., Inc.  
Rahway, N.J.

DEAR DR. TISHLER: It is my understanding that there are to be some congressional hearings related to the use of indomethacin in the treatment of rheumatoid arthritis. We are all cognizant of the difficulties involved in the evaluation—even double blind studies—of indomethacin or any drug in a disease such as rheumatoid arthritis which is characterized by exacerbations, remissions and the emotional component. However, I have found indomethacin to be a very useful drug in the treatment of rheumatoid arthritis, particularly in milder cases or in patients where one is reluctant to use corticosteroids as patients in the older age group and in those with diabetes, osteoporosis, etc. Furthermore, in the concomitant use of indomethacin with corticosteroids, the dosage of corticosteroids has been reduced in some patients.

Indomethacin has also been a very useful drug in the treatment of other types of rheumatic disease, i.e., episodes of acute gouty arthritis, bursitis, and osteoarthritis. In degenerative arthritis of the hips—for which we have so little to offer therapeutically—I have seen dramatic results from the use of indomethacin.

Sincerely yours,

NATHAN E. HEADLEY, M.D.,  
*Associate Clinical Professor of Medicine,*  
*U.S.C. School of Medicine.*

UNIVERSITY OF COLORADO MEDICAL CENTER.  
Denver, Colo., April 22, 1968.

Dr. MAX TISHLER,  
Merck Research Laboratories,  
Merck & Co., Inc.  
Rahway, N.J.

DEAR DR. TISHLER: I understand that hearings currently in progress, under the chairmanship of the Honorable Gaylord Nelson, are considering the drug Indomethacin (Indocin) and its value in the management of patients with rheumatoid arthritis.

I first undertook clinical investigation of this non-cortisone, anti-inflammatory agent in 1963, and first published our clinical studies of this drug in 55 rheumatoid patients in 1965 in the journal, Arthritis and Rheumatism. These clinical investigations were based upon the best objective measurements of rheumatic activity and at that time it was concluded that, "Indomethacin suppresses joint inflammation and improves function but may require up to 2 to 4 months to obtain maximum therapeutic effects". With three additional years of experience with this drug in more than 100 patients under rigid clinical observation and using similar methods of evaluation, I am still of this opinion.

To state how frequently favorable therapeutic effects occur based upon objective tests, and how often this drug is clinically beneficial is difficult, but in my opinion, between 20 to 25 percent do show objective changes; an additional 20 to 30 percent report subjective benefits.

Among the toxic reactions reported with the use of Indomethacin, the frequency of peptic ulceration has been of major concern to critical, clinical observers. An analyses of more than 700 patients treated with Indomethacin at the University of Colorado hospital and its clinics indicates that this complication seldom occurs. These patients had previously received other anti-inflammatory and analgesic drugs including aspirin, corticosteroids, and phenylbutazone. The incidence of peptic ulcers during the Indomethacin period of therapy was actually less than during similar periods of other anti-inflammatory, anti-rheumatic agents. In my experience, the occurrence of peptic ulceration is not a major obstacle to the clinical use of this drug in patients with rheumatoid arthritis.

In my five years experience based on the practical use of Indomethacin and a careful analysis of the results in all of our patients treated by a staff experienced in the management of patients with rheumatoid arthritis in this University Hospital, I am of the opinion that Indomethacin benefits some patients with rheumatoid arthritis. At present no reliable tests are available to predict which

patients with this chronic disease which is marked by spontaneous remissions and exacerbations, will respond favorable to this drug.

Until more potent and less toxic anti-inflammatory agents are made available for clinical use, I strongly recommend that Indomethacin continue to be available for use in this most crippling of all arthritic conditions. I would not discard a valuable tool although it might have a sharp edge.

Sincerely yours,

CHARLEY J. SMYTH, M.D.,  
Professor of Medicine,  
Head, Division of Rheumatic Diseases.

NORTHWESTERN UNIVERSITY,  
Chicago, Ill., April 22, 1968.

Dr. MAX TISHLER,  
Merck Research Laboratories,  
Merck & Co., Inc.,  
Rahway, N.J.

DEAR DR. TISHLER: As you know, we have been engaged during the last year in evaluating the efficacy of Indocin in patients with generalized osteoarthritis. In addition, we have used Indocin in the treatment of patients with other forms of arthritis particularly those of rheumatoid arthritis.

Although we do not have the results from our osteoarthritis study tabulated as yet, I would like to recall for you some of the difficulties that emerge from this type of work.

First, the cause of these types of arthritis is unknown. This means that one must utilize the symptoms the patient shows as clues concerning the response of the patient to treatment. It is not possible to state that a given causative feature has or has not been altered or changed by the treatment program. Such a statement concerning drug evaluation would of course be the best evidence for determination of an effective program.

This difficulty is further compounded by the variability of the course of these illnesses. It is very difficult to interpret the exact response of the patient to a drug or to no drug.

Therefore, to properly reach a conclusion about the efficacy of a drug requires a careful assessment of a number of signs and symptoms present in the disease and sufficiently large number of patients who are being evaluated.

Although gold treatment for rheumatoid arthritis has been used for almost four decades, it was only in the last few years that a carefully controlled drug study on the efficacy of this compound was completed by a group of British workers.<sup>1</sup> Even here considerable difficulty was encountered. I do not take the view that proper assessment is impossible but it certainly is difficult.

I think that it can be said that Doctor Mainland reached similar conclusions in his careful assessment of role of Indocin in rheumatoid arthritis. He did find it had a beneficial effect although no greater than aspirin. He also points out the real problems that beset any one who does drug evaluation studies.

In ordinary practice in our clinic we have been impressed by patients' response to Indocin in rheumatoid arthritis and other forms of arthritis, including osteoarthritis. We use the drug to help provide relief for patients who require additional medication besides aspirin.

It would be a tragic event if the demands for precision outstrip the methodology available. In our present state of ignorance one must accept less than optimal measure of effect. However, one constantly must try to improve the state of the art.

Sincerely yours,

FRANK R. SCHMID, M.D.,  
Associate Professor of Medicine,  
Chief, Arthritis-Connective Tissue Section.

TUCSON, ARIZ., April 22, 1968.

MAX TISHLER, Ph. D.,  
Merck Research Laboratory,  
Merck Sharp & Dohme,  
Rahway, N.J.

DEAR DOCTOR TISHLER: This is a testimonial letter in regard to Indomethacin (Indocin).

<sup>1</sup> Annals of Rheumatic Diseases, 19:95-117, 20:315-334, 1961.

My experience with this medication began with investigational studies starting in 1961, before this drug was released.

Subsequently, Indomethacin (Indocin) has become a most valuable medication in the treatment of various forms of rheumatic diseases.

Approximately one-half of my patients are receiving Indocin.

Cordially yours,

HARRY E. THOMPSON, M.D.

COLUMBUS MEDICAL CENTER  
RESEARCH FOUNDATION,  
*Columbus, Ohio, April 22, 1968.*

MAX TISHLER, Ph. D.,  
*Merck Research Laboratories,  
Merck & Co., Inc.,  
Rahway, N.J.*

DEAR DR. TISHLER: It is my understanding that you have been invited to appear before a Congressional hearing under the Honorable Gaylord Nelson to discuss the relative merits and clinical value of indomethacin, which is marketed under the brand name of Indocin. Since I originally introduced this drug to humans in November 1961, and have had as long and profound clinical experience with the drug as any physician in the world, I feel constrained to offer some comments.

It may be proper at this point to identify myself to you. As you may or may not know, I have been on the medical faculty of the Ohio State University for more than twenty-eight years and since 1960, have held the rank of Clinical Professor of Medicine. In addition, I am the Founder and Director of the Columbus Medical Research Foundation. I am also senior physician director of The Columbus Medical Center, which is a group-practice clinic of specialists in Diagnosis and Internal Medicine, with a heavy preponderance of rheumatic diseases. Three of the eight physicians (including myself) sub-specialize in the field of Rheumatology to the extent of having more than fifty percent of their practice devoted to that field. We have approximately five-hundred patients with rheumatoid arthritis on continuing active treatment and we regard Indocin as an important part of their overall drug-therapy program.

Not all patients with rheumatoid arthritis are benefited by Indocin, but the same can be said about all other antirheumatic drugs, even including cortisone-derivatives and aspirin. However, more than half of patients with rheumatoid arthritis receive decisive benefit from Indocin and are able to continue taking the drug without undue adverse effects; its record in this respect is superior to aspirin and second only to the benefits derived from cortisone-derivatives.

In over half of the patients who do benefit from Indocin the benefits are striking and decisive and the drug is regarded as indispensable to the patients continued well-being and disease-control. This variable, limited, and to some degree unpredictable response of Indocin in rheumatoid arthritis has led to opposite extremes of reaction in the minds of some physicians. Because it is not effective in considerably less than one hundred percent of the patients, some physicians call it a total failure, deny any value to it, and think it should be abandoned. Other physicians regard the striking benefits in some patients as proof that Indocin is a panacea and can be used to the exclusion of all other antirheumatic agents. Both of these extremes of viewpoint are ill-founded and unwarranted. The fact is that Indocin is an excellent adjunct in antirheumatic therapy and should be given a trial, beginning in low doses, in those patients with rheumatoid arthritis who have failed to respond to the so-called basic or conservative program of increased rest, physical therapy, salicylates and so forth.

Evaluation of drug efficacy in rheumatoid arthritis is a most difficult, profoundly complex and often unrewarding endeavor, best carried out by an experienced clinician-rheumatologist who has not only some acumen and scientific orientation, but also patience, understanding, empathy and a keen insight into the complexities of the rheumatoid personality, as well as the rheumatoid disease.

Unfortunately, there are no satisfactory criteria for evaluating rheumatoid disease activity with uniform and reliable consistency. The use of the "single-blind" placebo, by an experienced clinician, in a patient who has been on the drug under evaluation for some period is probably the most reliable method of approach to the problem and enables the clinician to evaluate the drug by

observing the patient's clinical response to the unknown substitution of placebo and to the unknown resumption of the active drug. Where emphasis is needed or where any doubt exists, the placebo trial can be repeated on a number of occasions in the same patient. The use of a placebo can also help the clinician to decide if the appearance of adverse effects or side reactions is drug-related. Oftentimes it is found that an adverse effect, thought to be drug-induced, was in truth the result of the patient's apprehension at taking part in an experiment.

In theory, the "double-blind" technique is the most desirable form of evaluation, but the non-clinician and the statistician fail to appreciate the numerous, often insurmountable difficulties in applying a "double-blind" study to a group of human patients. It is understandable that those who have done most of their work with testing in laboratory animals would want to carry-over this same methodology to the human, but it is becoming increasingly apparent from the reports of such statistician- and laboratory-oriented sources that the pitfalls of the "double-blind" study are manyfold and seem to increase exponentially with the increasing application of further controls and safeguards. Nevertheless, it may be advantageous for an experienced clinician to institute a "double-blind" study during the course of a therapeutic trial of a new drug, and derive important data from it.

In my many years of clinical experience with Indocin, I have used a number of "double-blind" trials, but I have not regarded them as having as much value to me as the hundreds of "single-blind" placebo trials which I carried out. The results of both, however, served further to convince me of the therapeutic efficacy of Indocin in the majority of patients with rheumatoid arthritis.

The Merck Company is to be congratulated for having labored so diligently to produce yet another effective drug for the treatment of this dread disease. I appreciate the opportunity to have developed the earliest clinical experiences with Indocin. However, the most important thing which I personally think makes your company especially deserving of commendation is the wholesome, objective, scientific atmosphere which all of the representatives of your company created and maintained throughout all my studies on Indocin. At no time were any pressures exerted on me in any manner or in any direction which could possibly have influenced my objective approach or created any prejudice or bias in my work or even in my thinking. At all times I felt completely free to report favorably or unfavorably and to state that in my opinion Indocin was good, bad or indifferent. In fact, at several stages I was hyper-critical of the drug and even now emphasize that it is not the last word in rheumatoid arthritis therapy, that improvements can probably be made with derivatives of the drug, that cerebral side-effects are a definite limitation, both in dosage ceiling and in more universal application of the drug. In this atmosphere I have developed the conviction that Indocin is a valuable drug and should not be denied to those patients with rheumatoid arthritis in whom it can and will produce decisive benefits.

Yours truly,

NORMAN O. ROTHERMICH, M.D.

BRONX, N.Y., April 22, 1968.

Dr. MAX TISHLER,  
Merck Research Laboratories,  
Merck & Co., Inc.,  
Rahway, N.J.

DEAR DOCTOR TISHLER: I am aware that there has been a discussion in the Congress through their appointed Committees to evaluate the evidence with regard to the therapeutic efficacy and the place in our pharmalogic armamentarium of Indomethacin.

The studies that we have performed and our current studies indicate that Indomethacin has an anti-inflammatory action, and through this anti-inflammatory action, a potent analgesic effect in the treatment of inflammatory connective tissue disease, particularly the inflammation associated with traumatic osteoarthritis. It appears to be of use in some patients with acute and chronic rheumatoid arthritis. Of course its effect in acute gout is well known.

The problem with Indomethacin has been the variable response to the drug. This is extraordinarily unusual, but offers a challenge as to the difference between this anti-inflammatory compound and the other which are available. Certainly, further research with Indomethacin and its analogues is warranted, and we are currently actively engaged in this research.

The question of the design of the studies for Indomethacin efficacy has been a challenge to us. A double blind study of Indomethacin against a sugar placebo

would produce no results since patients would be left for prolonged periods of time without medication, and if they were unfortunate enough to have the sugar placebo to continue in the study. In addition, there would be a discrepancy in the results between the possible carry over in the Indomethacin study which might have a greater effect with Indomethacin and a much less effect with the placebo. It would seem that an active medication would be indicated in the placebo capsules. We believe that aspirin answers this need.

With all of these considerations taken into account, I believe that a final evaluation with regard to Indomethacin efficacy should be postponed until all of the data from the studies that are now being carried out is collected. This will not only be more valuable with regard to Indomethacin, but will encourage further studies with Indomethacin analogues which are so important in the future.

Cordially,

JEROME ROTSTEIN, M.D.,  
F.A.C.P., F.C.C.P., Head, Rheumatic Disease Unit.

LOUISVILLE, KY., April 22, 1968.

Dr. MAX TISHLER,  
Merck Research Laboratories,  
Merck M. Co., Inc.,  
Rahway, N.J.

DEAR DR. TISHLER, This is a letter attesting to the efficacy of Indocin in my practice of rheumatology in Louisville, Ky.

This drug has been extremely effective in all of my patients with ankylosing spondylitis. As you well know, this is a very debilitating disease, which affects young men in their prime, and can be ruinous economically if the disease is not checked. In every one of my patients with ankylosing spondylitis, the disease has been checked either partially or completely. All of them are fulfilling, at present, useful lives.

Indocin has further more been effective in selected cases of osteoarthritis. In gout, Indocin has been very effective with minimal side effects. In rheumatoid arthritis, the drug has not been as effective as I would like, and I utilize it very little in these individuals.

For any sort of blind study to be done in individuals afflicted with these crippling diseases, I would consider it inhumane as well as immoral to deny benefits to a selected group of patients.

It would be my feeling, at present, that Indocin is a very effective drug in the conditions named, and there should be no question in its' efficacy in those individuals not only in suppressing their disease, but keeping them useful, productive citizens in our society.

If there is any further information you may require please contact me.

Cordially,

FRANK W. LEHN, M.D.

BOMBAY, April 22, 1968.

We had previously published the results of our experience with Indomethacin in rheumatoid arthritis and still feel that this drug represents a definite advance in treating many rheumatic diseases. Our experience confirms it to be a potent anti-inflammatory, analgesic and antipyretic agent, without many of the severe side effects of corticosteroids and butazones. We have used Indomethacin successfully in many cases who had not responded satisfactorily to aspirin and butazones. In rheumatoid arthritis, there is no doubt that requirements of corticosteroids can be substantially reduced and in a significant percentage of cases, these can be eliminated gradually. Side effects such as headache, giddiness and gastrointestinal irritation have occurred in about 40% of patients but it is not always necessary to discontinue therapy. Such side effects can be managed in the usual manner. We have not come across any case of blood dyscrasia, liver or renal damage.

K. K. DATEY, M.D.,

F.R.C.P. Honorary Professor of Medicine, Seth G.S. Medical College and King Edward Memorial Hospital; and Director, Department of Cardiology, King Edward Memorial Hospital, Bombay.

BRUSSELS, April 22, 1968.

Q.—In the light of your extensive experience in the management of diseases for which Indomethacin is indicated, do you consider that the introduction of Indomethacin has contributed to the management of your patients?

A.—Yes—in osteoarthritis of the hip, in Bechterew's disease and in rheumatoid arthritis in association with gold therapy.

Q.—Do you find that Indomethacin enables you to obtain results in some of your patients that were difficult to obtain prior to its introduction?

A.—Yes—in osteoarthritis of the hip and Bechterew's disease because the toxicity of Indomethacin on long-term treatment is lower than the toxicity of other available drugs.

Q.—If so, can you define those areas in which the drug has been most helpful to you?

A.—Osteoarthritis of the hip and spondylitis rhizomelica.

Prof. Dr. L. J. Michotte.

BOMBAY, April 22, 1968.

I have been using indomethacin in the form of capsules as well as suppositories since the last five years. In my experience, indomethacin has proved to be a valuable drug for treating rheumatoid arthritis and allied disorders. A number of my patients who had not responded to salicylates, phenylbutazone or oxyphenbutazone were maintained satisfactorily on indomethacin. I have studied the drug's steroid-sparing properties carefully and am convinced that the dosage of corticosteroids can be gradually reduced in a large percentage of cases. I have also tried the drug for prolonged periods in Still's disease where it works most satisfactorily and has excellent tolerance. Indomethacin suppositories have been used in my department in 16 patients for almost two years continuously. Patients having gastrointestinal problems with capsules can be managed remarkably well on indomethacin suppositories.

M. M. DESAI, M.D.

M.R.C.P., F.C.P.S., Honorary Associate Professor of Medicine, Topiwala National Medical College and B.Y.L. Nair Hospital; Physician In-charge, Department of Rheumatic & Collagen Diseases, B.Y.L. Nair Hospital, Bombay.

RHEUMATISM RESEARCH UNIT,  
CANADIAN RED CROSS MEMORIAL HOSPITAL,  
Taplow, Maidenhead, Berks, April 22, 1968.

DR. MAX TISHLER,  
President, Merck, Sharpe Dohme Research Laboratories,  
Rahway, N.J.

DEAR DR. TISHLER, Dr. Carl Pearson of Los Angeles has let me know that there are to be some Congressional hearings in relation to Indomethacin (Indocin). I regret that I shall not be able to come over, but instead he suggested that I might write you in general terms about our experience with this drug both here and at the Royal Postgraduate Medical School. We have not performed any controlled trials, so that what follows is the result of clinical observation.

I feel that this drug is useful in certain patients with rheumatoid arthritis and has about the same potency as aspirin. It is, however, more expensive and we therefore tend to use it when patients cannot tolerate aspirin and sometimes to wean them off steroid medication. This we have been able to do satisfactorily. It seems useful also in ankylosing spondylitis, and we have used it there in such cases who have developed intolerance to phenylbutazone. It appears to be of some value in osteoarthritis of the hip. I have not used it in gout.

We have used Indocin in over 30 children in the first two decades with chronic polyarthritis and it has seemed quite useful here, except perhaps in the youngest children, in whom it has induced vomiting. In general we have not had a great deal of trouble with side effects, apart from headache. We have had one case with perforation of the stomach and two with melaena. Two of our patients have had a rather odd reaction mentally which has ceased on stopping the drug.

Since, however, we have had no control series, it is difficult to evaluate these complications, since, as you well know, some such effects occur even on placebo. We think, however, that these were probably related to the drug.

I hope this is the information you require.

Yours sincerely,

E. G. L. BYWATERS, F.R.C.P.,

(Professor of Rheumatology, University of London,  
Hon. Director, Medical Research Council Rheumatism Research Unit).

[Telex received in New York from Milan]

APRIL 22, 1968

**Dr. M. TISHLER,  
Rahway:**

Prof. D. Gigante—Director of Rheumatological Institute of University of Rome—stated today—The introduction of Indomethacin has greatly contributed to the management of patients with rheumatic disease.

Corticosteroids still remain the most effective drugs for the treatment of many rheumatic patients. However Indomethacin has enabled me to treat effective a large number of these patients because of its marked anti-inflammatory properties which are generally not accompanied by the occurrence of serious side effects.

Indomethacin has been most helpful in the treatment of the following diseases—gout, degenerative disease of the hip and Ankylosing Spondilitis. It has been also very effective in a great number of patients with rheumatoid arthritis.

Copy of above statement signed by Gigante will be airmailed.

[Message received in New York from Milan]

APRIL 23, 1968.

**Dr. MAX TISHLER,  
Rahway:**

Following statement by Prof. C. B. Ballabio, Director of Rheumatological Institute of the University of Milan—"Without doubt the introduction of Indomethacin has contributed to the management of my rheumatic patients. In degenerative disease of the hip Indomethacin gives excellent results which were not possible to obtain with any other medication.

The rheumatic diseases which in my experience can be treated most effectively with Indomethacin alone or sometimes in association with other medications are ankylosing spondylitis and gout. Indomethacin is of some help in the treatment of some rheumatoid arthritis patients especially males."

Copy of above statement signed by Ballabio will be airmailed.

[Telex received from Hoddesdon in New York]

APRIL 23, 1968.

**Dr. M. TISHLER,  
Rahway:**

Indomethacin contributes to the management of rheumatoid arthritis. It enables some patients to be controlled who have not previously been controlled. Watson Buchanan Head of the Centre of Rheumatic Diseases, Glasgow.

Regards,

HODGKINSON.

BUENOS AIRES.

Tishler Dr. Romanowicz report head of Rheumatology Rheumatic Disease Center, Rawson Hospital answer first question yes Indocid is of great utility, second, yes, third, rheumatoid arthritis arthrosis gout ankylosing spondylitis unspecific arthritis.

MASANTI.

CAPE TOWN, April 23, 1968.

Question: In the light of your extensive experience in the management of diseases for which Indomethacin is indicated, do you consider that the introduction of Indomethacin has contributed to the management of your patients?

Answer: Yes.

*Question:* Do you find that Indomethacin enables you to obtain results in some of your patients, that were difficult to obtain prior to its introduction?

*Answer:* Definitely yes.

*Question:* If so, can you define those areas in which the drug has been most helpful to you?

*Answer:* Resistant cases of rheumatoid and osteoarthritis gout.

DR. R. A. ASHERSON.

#### STATEMENT ON INDOMETHACIN BY DR. SELWYN NELSON

This statement is made on the understanding that no use is made of it which is likely to be unethical or embarrassing to the writer.

Indomethacin is a valuable addition to the range of preparations available for the treatment of rheumatic diseases.

All drugs used in the long term management of rheumatic diseases are likely to cause unwanted effects in some patients and Indomethacin is no exception. Most if not all of the toxic effects of Indomethacin are rapidly reversible and also are obvious to the patient.

In the choice of treatment of rheumatic diseases the clinician takes into account the properties of the drug and his experience of its effectiveness in various conditions, its toxicity and the incidence and reversibility of possible unwanted effects. He also takes into account the contra-indications having regard for the expected effect of the drug on a patient suffering from other disorders related or unrelated to the primary condition being treated.

The approach to the prescribing of Indomethacin can be based on a positive or negative assessment of the patient's needs. Experience with Indomethacin has demonstrated its very great effectiveness in gout, rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. It is also very useful in certain miscellaneous non-specific painful disorders of the musculo-skeletal system e.g. Bursitis, "fibrositis" etc. This might be termed the positive approach.

As Indomethacin has a different chemical composition from other non-steroidal anti-inflammatory drugs it can be used where other preparations have been tried and found wanting.

Indomethacin can be used in preference to other anti-inflammatory drugs where there has been a previous toxic effect on the bone marrow caused by another preparation. It is also valuable in the presence of reduced cardiac reserve as it does not cause retention of salt and fluid.

#### [Translation]

Dr. Pedro M. Catoggio, Director of the National Institute of Rheumatology, National Institute of Rheumatology, Martinez de Hoz y Marconi—Ramos Mejia, Peia. Bs. As., Rep. Argentina :

(1) Question : In the light of your extensive experience in the management of diseases for which indomethacin is indicated, do you consider that the introduction of indomethacin has contributed to the management of your patients?

*Answer:* Yes

(2) Question : Do you find that indomethacin enables you to obtain results in some of your patients that were difficult to obtain prior to its introduction?

*Answer:* Yes

(3) Question : If so, can you explain those areas in which the drug has been most helpful to you?

*Answer:* Rheumatoid arthritis, acute inflammatory exacerbations in arthrosis, periarthritis, and in acute gout and rheumatoid spondylitis I have little experience.

Comments : (1) In the last few months we have used suppositories more frequently, (2) We often made the association with ASA, corticosteroids or anti-malaric drugs (in R.A.)

#### [Translation]

Dr. Raul Houssay, Rheumatologist of the Department of Rheumatology, Ward 20, Rivadavia Hospital, Sanchez de Bustamante 2560, Buenos Aires, Rep. Argentina :

(1) Question: In the light of your extensive experience in the management of diseases for which indomethacin is indicated, do you consider that the introduction of indomethacin has contributed to the management of your patients?

Answer: Indomethacin contributes to the management of rheumatic patients for its analgesic action and when the effective dose is well tolerated.

(2) Question: Do you find that indomethacin enables you to obtain results in some of your patients that were difficult to obtain prior to the introduction?

Answer: Indomethacin enables me to obtain good results in some patients in which the necessary doses of other drugs for the obtention of satisfactory analgesic and anti-inflammatory effects are not tolerated.

(3) Question: If so, can you explain those areas in which the drug has been most helpful to you?

Answer: (a) Osteoarthritis. Arthrosis of the hip, (b) Rheumatoid spondylitis, (c) Nonarticular rheumatisms (painful shoulder, bursitis, fibrositis, etc.), (d) Rheumatoid arthritis: Indomethacin is effective in some patients with R.A., especially if it is administered in combination with other medications. Indomethacin is useful for the treatment of morning stiffness.

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[Translation]

Dr. Osvaldo Hübscher, Rheumatologist of the Department of Rheumatology, Ward 20, Rivadavia Hospital, Sánchez de Bustamante 2560, Buenos Aires, Rep. Argentina:

(1) Question: In the light of your extensive experience in the management of diseases for which indomethacin is indicated, do you consider that the introduction of indomethacin has contributed to the management of your patients?

Answer: Yes; in some patients. Indomethacin has analgesic and anti-inflammatory action. It can be administered for a long time without important danger.

(2) Question: Do you find that indomethacin enables you to obtain results in some of your patients that were difficult to obtain prior to its introduction?

Answer: Yes. In some patients the addition of indomethacin to the previous treatment or its substitution, enables the physician to obtain a better management of the patients. In other patients indomethacin has no action.

(3) Question: If so, can you explain those areas in which the drug has been most helpful to you?

Answer: (a) In rheumatoid arthritis: generally associated to other drugs. Without doubt it has a steroid sparing effect. The use of suppositories at bedtime improves the morning stiffness of the patients, (b) In osteoarthritis with inflammatory signs, (c) In rheumatoid spondylitis, (d) Lower action in fibrositis, tendinitis and other unspecified conditions, (e) No experience in acute gout.

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[Translation]

Dr. Armando Maccagno, Head of Clinics, Rheumatic Diseases Center, Ward 14, Rawson Hospital, Buenos Aires, Republica Argentina:

(1) Question: In the light of your extensive experience in the management of diseases for which Indomethacin is indicated, do you consider that the introduction of Indomethacin has contributed to the management of your patients?

Answer: Yes

(2) Question: Do you find that Indomethacin enables you to obtain results in some of your patients that were difficult to obtain prior to its introduction?

Answer: Yes

(3) Question: If so, can you explain those areas in which the drug has been most helpful to you?

Answer: *Rheumatoid arthritis, Rheumatic spondylitis, Intermittent hydrarthrosis.*

*Arthrosis:* Only in the first and second period. In period 3 I prefer surgical treatment.

In *gout* I have not much experience; in these patients I prefer phenilbutazone because it has uricosuric effect. Only when phenilbutazone is ineffective I use Indomethacin.

I think that the combination Indomethacin-Dexamethasone is very effective because Indomethacin has a steroid sparing effect and the action of both drugs is potentiated.

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[Translation]

Dr. Osvaldo García Morteo, Head of Rheumatology, Rheumatological Department, Ward 20, Rivadavia Hospital, Sánchez de Bustamante 2560—Buenos Aires—Rep. Argentina, Secretary of the Argentine Society of Rheumatology:

(1) Question: In the light of your extensive experience in the management of diseases for which indomethacin is indicated, do you consider that the introduction of indomethacin has contributed to the management of your patients?

Answer: In some rheumatic conditions the introduction of indomethacin has contributed to the management of the patients. In some patients with rheumatoid arthritis it has been able the use of lower doses of corticosteroids and sometimes it was possible the withdrawal of these drugs. In patients with acute inflammatory exacerbations may be a good approach.

(2) Question: Do you find that indomethacin enables you to obtain results in some of your patients that were difficult to obtain prior to its introduction?

Answer: Yes. Some patients have a therapeutic response not obtained previously with other anti-rheumatic drug. Is useful in rheumatoid spondilites and in some inflammatory conditions of the soft tissues. Irregular results were obtained in acute gout. Sometimes indomethacin is ineffective.

(3) Question: If so, can you explain those areas in which the drug has been most helpful to you?

Answer: Its possibility of long time administration made of indomethacin, a drug which is useful in the treatment of R.A. and osteoarthritis. The administration of indomethacin, when the patient goes to bed produce an improvement of morning stiffness. Indomethacin is better tolerated when is administered by rectal route than by oral route.

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[Translation]

Dr. Ana Porrini, Rheumatologist of the Department of Rheumatology, Ward 20, Rivadavia Hospital, Sánchez de Bustamante 2560, Buenos Aires, Rep. Argentina:

(1) Questions: In the light of your extensive experience in the management of diseases for which indomethacin is indicated, do you consider that the introduction of indomethacin has contributed to the management of your patients?

Answer: Yes.

(2) Question: Do you find that indomethacin enables you to obtain results in some of your patients that were difficult to obtain prior to its introduction?

Answer: Yes.

(3) Question: If so, can you explain those areas in which the drug has been most helpful to you?

Answer: (a) In R.A.: Sometimes alone, associated to a basic plan of treatment which includes ASA, exercises and resting. Sometimes it is possible the reduction of steroid drugs.

(b) In Osteoarthritis.

(c) In Rheumatoid spondilitis: In my opinion, phenilbutazone is the selected drug in this condition but, however, I think that indomethacin is more useful in this case.

(d) In non articular rheumatic conditions: specially tendinitis of the shoulder and dorsal and lumbar fibrositis.

(e) In gout: In acute gout the results were not satisfactory; in these patients there were important side effects attributable to the use of high doses. Good results were found in some patients with chronic gout.

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CAPETOWN/KAAPSTAD,  
April 23, 1968.

I have not had the facilities to conduct controlled studies of Indomethicin, but from 1964 I have had an extensive experience with this drug in the Arthritis Clinic of the Teaching Hospital of the University of Cape Town as well as in private practice.

Side effects were common at the outset because the dosages recommended proved to be too large. Moreover side effects were for the most part unpleasant but were not danger signals. The possible exception in gastero-intestinal complications which are in the first place rare and in the second place it is difficult to establish a cause and effect relationship. More often than not such patients were receiving other anti-rheumatic preparations as well e.g. Salicylates.

Indomethacin has proved of value the treatment of Gout, Osteo-Arthritis and Rheumatoid Arthritis. In the last named it is especially useful as a steroid sparing agent.

T. J. DRY, M.D.

WIESBADEN, 26.4.1968.

Re Indomethacin.

Dr. MAX TISHLER,

*Präsident der Merck Sharp u. Dohm  
Vis. Laboratories Rahway, N.J.*

DEAR DR. TISHLER: Since 1964, indomethacin has been tested clinically and prescribed regularly at the clinic for rheumatic diseases in the Kaiser-Friedrich Spa Wiesbaden. Indomethacin is indicated in rheumatic and related diseases. In antipyretic therapy indomethacin has proved to be a valuable drug for supplementing already established anti-inflammatory agents. Indomethacin was shown to be useful in certain cases and forms of rheumatoid arthritis, arthrosis deformans, Bechterew's disease (rheumatoid spondylitis) after the other, non-hormonal anti-inflammatory agents had failed. Our experiences are confined to rheumatic and related diseases. The drug, which has meanwhile become a frequently used standard preparation, was not given in other indications.

Very truly yours,

DR. MIEHLKE, *Chief-of-Staff.*

BALTIMORE, Md., April 23, 1968.

Dr. MAX TISHLER,

*Merck Research Laboratory,  
Merck & Co., Inc.,  
Rahway, N.J.*

DEAR DR. TISHLER: I understand that there are to be hearings on the drug Indocin before a senate subcommittee in the near future.

My letter is to let you know that I have found Indocin very helpful in a limited number of arthritics who have not responded to other medication, such as aspirin, Butazolidin and Tandearil. There are a small number of people with rheumatoid arthritis who do extremely well on Indocin, and if they respond, they respond to doses of 75 mg. a day or less.

Although there is a great deal of emphasis placed on so-called double-blind studies of antirheumatic drugs by the American Rheumatism Association and its Study Group, I have found that this type of study is not essential to determining whether a drug has a beneficial effect in a rheumatoid arthritic who has been under my care for a long time.

To quote Dr. Fuller Albright, under whom I had the privilege of working for one year in 1941-42 in Boston, one patient well studied is worth 100 patients poorly studied. My patients with rheumatoid arthritis are well studied and well followed and I can tell when they receive benefit from a drug.

I believe that Indocin is a valuable addition to our therapeutic armamentarium in managing patients with this disease. I have also found it of value in a few patients with ankylosing spondylitis who have failed to respond to Butazolidin.

Very sincerely,

HARRY F. KLINEFELTER, M.D.

BUFFALO, N.Y., April 23, 1968.

Dr. MAX TISHLER,

*Merck Research Laboratory,  
Merck & Co., Inc.,  
Rahway, N.J.*

DEAR DR. TISHLER: In view of the impending Congressional hearing concerning the results of Indocin (Indomethacin) treatment of arthritis, I believe that the conclusions of "clinically" oriented rheumatologists and their numerous patients are just as important as the results of "double blind" studies which have been

reported by "statisticians" or "full time" physicians who treat a small number of patients with rheumatic diseases. While I admit that "double blind" studies are desirable, there are many possible errors that are not included in the statistical analysis of these studies and the results are used only to depreciate the potential values of the drug under test. This is especially true in the case of patients with rheumatoid arthritis, where the disease process is extremely variable from day to day, or week to week status; where short term evaluation of drug effect is inaccurate (in a few weeks); when patients are allowed to use a variable amount of aspirin; and where only objective measurements of joints are the decisive criteria. In the majority of rheumatoid patients in any one study, whether "double blind" or "uncontrolled," irreversible changes that determine size of joints, range of motion, and discomfort, have already occurred and do not improve particularly in a period of a few weeks. Such changes are not due to the active inflammatory process of the disease but are the result of long continued disease. The resultant "mechanical" disturbance of joint components cannot be corrected by anti-inflammatory drugs, whether they are salicylates, anti-malarials, phenylbutazone, or indomethacin. However, the statisticians and the "purists" decry the lack of objective measurements of improvement and completely disregard the subjective response of the patient. I will admit that none of the anti-inflammatory drugs mentioned above, have the prompt, dramatic response as the cortico-steroids but they do not have the serious toxicity associated with their "long term use."

After more than 20 years of experience in the exclusive treatment of rheumatic patients, I do not subscribe to the conclusions of Short & Bauer that 50% of rheumatoid patients improve with the most conservative treatment. Another frequently quoted "double blind," "cross over" trial with an anti-malarial drug, which was regarded as a masterpiece of drug testing and demonstrated the unquestionable response to the drug, is no longer considered as a "drug of choice" by most clinical rheumatologists. This decision has been determined by the nebulous response of most patients both subjectively and objectively, plus the possible occurrence of irreparable eye damage which was impossible to determine during the short period of the study.

I have used Indomethacin in the therapy of the rheumatic diseases in more than one thousand patients in the past 6 years. In my experience, it has been an effective drug in the majority of these patients and has contributed one more effective drug to the treatment of various rheumatic conditions, which have been a most difficult problem, not only to the physician, but more importantly to the patient. On the basis of carefully controlled animal experiments in the laboratory and also by reduction of fever and inflammation clinically in the patient with acute arthritis, there can be no dispute that Indomethacin is a potent anti-inflammatory drug. There is no question throughout the world that Indomethacin is one of the most effective drugs in relieving such conditions as acute gouty arthritis, acute tendonitis, ankylosing spondylitis, and degenerative (osteoarthritis) joint disease of the hip. The only dispute has centered about the question of response in patients with rheumatoid arthritis, which even the "statisticians," the "purists" and the "reviewers" admit is subject to remissions and exacerbations, difficult to evaluate, and that Indomethacin is at least comparable to phenylbutazone and aspirin.

Indomethacin is of benefit to a variable degree in at least 66% of the patients in my experience. Subjective response has been better maintained with this drug than with either phenylbutazone or salicylates in the chronic arthritic patients (either rheumatoid or degenerative joint disease). The majority of these patients have continued to use the drug (many since 1962) for more than 3 years, which I believe in itself is a testimonial that the drug is effective. Many of this group have been challenged with a placebo or have voluntarily discontinued the drug, even replacing it with a high salicylate dose. However, they have reported a prompt flare of their symptoms and have resumed Indomethacin therapy in practically all instances. The drug has produced functional improvement in many patients, even in patients with mechanical damage to their joints. In early rheumatoid patients with inflammation and joint swelling, I frequently observe decrease (and even complete subsidence in some patients) of the joint inflammation. The results of long term administration in this group of patients will be published in the proceedings of the 2nd Laurentian Conference on Rheumatology (Nov. 1966) which I understand is in press at this time.

It has also, been my experience that 50% of rheumatoid patients on corticosteroid therapy have been able to reduce the steroid when Indomethacin has been added to their therapy. Toxicity remains within tolerable limits in my experience

and I have not encountered any unusual new reactions with its continued use. Side effects on the gastro-intestinal tract, headaches, dizziness, or a feeling of confusion continue to be the common complaints in my experience.

Sincerely yours,

BERNARD M. NORCROSS, M.D.

MINNEAPOLIS, MINN., April 23, 1968.

MAX TISHLER, Ph. D.,  
*Merck Research Laboratories,*  
*Merck & Co., Inc.,*  
*Rahway, N.J.*

DEAR DR. TISHLER: I am writing this letter to place on record my opinion that Indomethacin is an effective anti-rheumatic agent. Although, my own clinical research published in 1964, plus a fairly extensive experience with Indomethacin since then does not indicate a major anti-inflammatory effect in rheumatoid arthritis, the drug is useful in many such patients. But without doubt Indomethacin is of great benefit in patients with ankylosing spondylitis, Reiter's disease, psoriatic arthritis, and acute gout. Its benefit in these later patients is so unequivocal that a double-blind trial is, I believe, unnecessary and likely redundant. The few negative reports should not out weight the preponderant positive evidence of the usefulness of this drug.

Sincerely,

PAUL J. BILKA, M.D.

LOUISVILLE, KY., April 23, 1968.

Dr. MAX TISHLER,  
*Merck Research Laboratories,*  
*Merck, Inc.,*  
*Rahway, N.J.*

DEAR DR. TISHLER: I have been asked to comment on the evaluation of drugs in rheumatoid arthritis, and the question of effectiveness of indomethacin.

I am enclosing a reprint of one of my papers published in the J.A.M.A. Although my remarks related to the difficulty in assessing the effects of drugs in rheumatoid arthritis were written with special regard to corticosteroids, I think they remain pertinent to the present question. (See bottom of page 1254 under heading "Rationale of Procedure" and top of page 1254 as marked.)

Concerning indomethacin, my feeling is that this compound is effective in acute gouty arthritis and ankylosing spondylitis. Response in rheumatoid arthritis is not predictable without clinical trial but certain rheumatoid patients seem to derive benefit.

I hope this information will be useful.

Sincerely,

DAVID H. NEUSTADT, M.D.,

*Associate Clinical Professor of Medicine, Chief, Section on Rheumatic Diseases, University of Louisville School of Medicine.*

[From J.A.M.A., July 11, 1959, p. 1254]

#### RATIONALE OF PROCEDURE

There is no completely reliable plan or method of evaluating a new agent in rheumatoid arthritis that is not associated with certain shortcomings. To control all variables that come into play in a chronic disease of unknown origin subject to spontaneous fluctuations is a problem which has recently received well-deserved attention.

Short-term observations may be misleading. However, if one omits patients from a study who received a drug for short periods, one may be accused of influencing the final statistical results. Also there may have been some important reason for withdrawing the drug early in the study.

Double-blind and random selection studies are considered by some to disclose results of greater scientific precision than the older and more conventional type of evaluation study. However a double-blind technique also carries with it certain disadvantages that may compromise its value. In conducting studies with a relatively inactive drug (slowly acting agent), such as an antimalarial agent or a gold salt, a double-blind study can be carried out. When employing a corticosteroid which has powerful suppressive capacity, abrupt withdrawal and

placebo substitution is immediately noticed by the majority of patients. Sudden discontinuance also is not without danger because of the possibility of producing a marked degree of adrenal insufficiency. This hypoadrenal state can become an acute and serious medical emergency. Also random selection introduces a number of patients who may be unreliable and are not suitable for testing. Thus, it is almost impossible to carry out such a program without both influencing patients and introducing added difficulties.

For these reasons patients were carefully screened to include only those with well-established rheumatoid arthritis of over one year's duration and to exclude hyperreactors, unreliable patients, and hypersensitive ones.

OCHSNER CLINIC,  
New Orleans, La., April 23, 1968.

Dr. MAX TISHLER,  
*Merck Research Laboratory,*  
*Merck & Co. Corp.,*  
*Rahway, N.J.*

DEAR DR. TISHLER: Recently it has come to my attention that a Congressional body was considering a recommendation that Indocin be removed from the open market and reclassified so that additional double blind studies could be carried out in attempting to establish its role in the treatment of arthritis.

I had the opportunity to prescribe Indocin in the earlier days when it was available in tablet form, and, of course, was not impressed by the results that we obtained. When the new physical changes were made, and it was furnished in capsule form, I gained the impression that it offered symptomatic relief and in some cases favorable objective changes in a significant number of arthritic patients.

At least 95% of my practice deals with arthritic patients; I have had occasion to prescribe for these sufferers for many years and have now placed Indocin as a valuable drug adjunct in the therapeutic armamentarium.

Patients whom I see comprise a group that I have had an occasion to watch for many years and, as I have maintained in the past, it is only after observing arthritic patients over a minimum of a three year span am I able to gain some insight into what pattern the disease may follow. Realizing this, I appreciate that drug response varies from patient to patient.

My personal conclusions are that Indocin is of definite symptomatic benefit in a large group of patients with arthritis. Gouty patients obtained significant relief from their acute gouty pain when Indocin is administered and the chronic gouty arthritic who is unable to take aspirin medication or Butazolidin will frequently be very thankful because Indocin relieves them of their chronic, nagging joint aches. They can continue to take Indocin without it interfering with uricosuric drugs or where geographic location makes it unable to obtain blood counts that must be used to guide treatment with Butazolidin. This also is an economic factor when repeated lab studies must be carried out in patients who are given an agent such as Butazolidin.

Ankylosing spondylitis and osteoarthritis of the spine frequently cause patients a considerable amount of pain and incapacitation and Indocin has proven very helpful for these patients, and it is my opinion that it has kept many of these people on the job or in school.

Other types of non-specific rheumatism, such as bursitis, tendinitis, and giant cell arteritis, also seem to respond symptomatically and the patients are thankful for having such an agent available.

In rheumatoid arthritis the drug gives a certain number of patients a significant amount of subjective relief, allowing them to carry out the arthritis exercises and other basic parts of their treatment. Here, too, I feel that the comfort obtained allows them to carry on with their daily obligations and lead a more normal life. It seems to offer an adjunct to aspirin medication, which is our best antirheumatic drug, and does not seem to interfere with other agents, such as gold salts. It also has allowed me to reduce the quantity of adrenal steroids that some patients seem to require to remain functional. I have watched patients use Indocin long enough that occasionally they are under the impression that the drug is no longer giving them any beneficial effect and they discontinue its use on their own, or request permission to discontinue it, and more often than not they find that resuming the drug does give them an added benefit. I find that the symptomatic response to Indocin is often unpredictable for the rheumatoid arthritic patient.

The toxic effect of the agent is appreciated, but to date I do not recognize that it is any more irritating to the stomach than Butazolidin or aspirin and the other annoyances, such as headache, dizziness, etc., are transient and disappear once the drug has been reduced.

I am familiar with the published articles that question the value of Indocin, but I do not feel that double blind studies necessarily reflect the true value of a drug for stages of these diseases change, and only by watching patients for many years can we evaluate a drug response.

In my mind and those of my associates, this drug is of value for the arthritic patient and we would feel that it would do the patients an injustice to remove it from the market at this time, and in my own mind I question how long double blind studies would have to be carried out before they would be effective and meaningful. It seems that any double blind study would take at least ten years and the evidence against the drug does not validate such a move.

Yours truly,

THOMAS E. WEISS, M.D.

LOUISVILLE, KY., April 23, 1968.

Dr. MAX TISHLER,  
Merck Research Laboratories,  
Merck & Co., Inc.,  
Rahway, N.J.

DEAR DR. TISHLER: It has come to my attention that a congressional committee is investigating the drug Indocin (indomethacin).

I should like to state that there are many clinical indications for its use, certain situations where it is the drug of choice and that these comments are borne out by experience with a variety of disease entities.

Sincerely,

WILLIAM P. PEAK, M.D.

HENRY FORD HOSPITAL,  
Detroit, Mich., April 23, 1968.

Dr. MAX TISHLER,  
Merck Research Laboratories, Inc.,  
Rahway, N.J.

DEAR DOCTOR TISHLER: I have learned the Nelson Committee is investigating the efficacy of Indocin. In view of these developments, I thought you might be interested in our comments.

It has been our experience that Indocin is both antiinflammatory and anti-rheumatic. It has been a useful adjunct in the management of patients with osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and gout. In some instances of hypercorticism, it has been a useful antirheumatic agent when steroids were withdrawn.

Although the antirheumatic and anti-inflammatory effects of Indocin may be unpredictable, Indocin has been a welcome addition to our armamentarium.

Sincerely yours,

JOHN W. SIGLER, M.D.,  
Chief, Division of Rheumatology.

NEW YORK, N.Y. April 23, 1968.

Dr. MAX TISHLER,  
Merck Research Laboratories,  
Merck & Co., Inc.,  
Rahway, N.J.

DEAR DR. TISHLER: I have been informed that the Nelson Committee is considering Indocin, and one of the points under consideration is that it is no more effective than Aspirin in the treatment of rheumatic disease. To date, I have administered Indocin to more than four hundred patients. I have also had the occasion to compare the results of Indocin with a number of Aspirin preparations.

I was doing a double blind test on various preparations of Aspirin and a number of patients were taken off of Indocin to be included in this Aspirin study after two weeks without medication. These patients, after finishing the Aspirin study and another two week period without medication, were again returned to the Indocin. I was aware at the time that there had been a question raised as to whether Indocin was more effective than Aspirin. I, therefore, was interested

in the clinical comparison and, in my opinion, Indocin is definitely superior to Aspirin in the treatment of various forms of rheumatic disease. It, of course, does not control every case but it does help a great many where Aspirin fails to do so.

I am also fully acquainted with the Mainland report, and I think the criteria used are unrealistic and do not give a real evaluation of the drug being studied.

Sincerely yours,

WILLIAM B. RAWLS, M.D.

ARTHROSIS REHABILITATION CENTER,  
Washington, D.C., April 23, 1968.

Dr. MAX TISHLER,  
Merck Research Laboratories,  
Merck & Co., Inc.,  
Rahway, N.J.

DEAR DOCTOR TISHLER: I am writing you about our experiences with Indomethacin when used as a therapeutic agent in the management of patients suffering from rheumatoid arthritis. First, let me say that our practice is limited to the diagnosis and treatment of patients with arthritis and rheumatic diseases, that we register over one hundred new cases of rheumatoid arthritis every year and that we have not less than two hundred cases of that condition under close observation at all times. I have checked my Diagnosis File and find that since I first opened an office in 1937, a diagnosis of rheumatoid arthritis has been made in 2,043 patients.

Against the above background, it is my opinion that Indomethacin is an extremely valuable agent in the management of this potentially disabling condition and that it has been an important addition to our medical armamentarium. Thus, we have found patients who did not respond to aspirin, phenylbutazone or oxyphenbutazone, who did respond to Indomethacin. By "respond", I mean that the patients would note less pain and stiffness while the physician would observe lessening of the swelling and increase in the motion of involved joints. Furthermore, patients who have originally shown response to aspirin or one of the other drugs, may later become resistant to that drug and then respond to Indomethacin.

Of course, the reverse is also true and some patients who respond to aspirin and phenylbutazone or oxyphenbutazone will not respond to Indomethacin and some of those who do respond to Indomethacin will later become resistant to it.

I confidently hope that the day is not too far off when we will have a "cure" for rheumatoid arthritis. However, no "cure" is known today, and we must therefore use every therapeutic modality available in our fight against this chronic and too often devastating disease. Any drug which will help retard the condition—even if only for a time—is one to be used as long as it brings about relief. In this context, Indomethacin has earned its place as an agent which should be available to any physician treating rheumatoid arthritis.

Very sincerely,

DARRELL C. CRAIN, M.D.

THE LANKENAU MEDICAL BUILDING,  
Philadelphia, Pa., April 24, 1968.

Dr. MAX TISHLER,  
Merck Research Laboratories,  
Merck & Co., Inc.,  
Rahway, N.J.

DEAR DOCTOR TISHLER: I have been recently advised of the question which has been brought up regarding the efficacy of Indocin. I would like to have the privilege of speaking to this.

Indocin has been extremely helpful in my practice in the management of a multiplicity of problems. I have a large pure rheumatologic practice. A rough estimate of my experience with Indocin would include approximately thirty rheumatoid spondylitics, perhaps 200 rheumatoid arthritics and innumerable osteoarthritis and gouts. I am amused by the remarks I recently read regarding the need to do double blind studies with Indocin. There can be absolutely no equivocation as to the efficacy of Indocin in a host of rheumatic disease. After fifteen years of a practice limited to rheumatology one cannot make mistakes

of this type. This is so emphatically evident in the rheumatoid spondolytic that I consider this observation, though it may not be effective, an enormous joke; however, misleading the public, medical lay is dangerous and grave enough a situation to prompt me writing you.

Indocin is certainly not effective in all, in fact a much smaller percentage of my patients than I had hoped, and it has some unhappy side effects which require careful observation, but it must be perfectly evident that I would find it very difficult to practice rheumatology without this valuable arm.

I should be happy to provide statistics if you care for them.

Very truly yours,

ERNEST M. BROWN, Jr., M.D.

MAYO CLINIC,

Rochester, Minn., April 24, 1968.

MAX TISHLER, Ph. D.,  
President, Merck Sharp & Dohme  
Research Laboratories,  
Rahway, N.J.

DEAR DOCTOR TISHLER: It has been brought to my attention that the matter of the effectiveness of indomethacin may be questioned at a future congressional hearing on drugs. As a rheumatologist, I have had considerable experience with the use of indomethacin in patients with a wide variety of rheumatic diseases and I would be most distressed if this drug were not available for use in appropriate rheumatic diseases. I have found that many patients derive helpful relief of rheumatic symptoms from indomethacin, relief which often has not been obtainable with other simple analgesic medications. As is the case with all of the anti-rheumatic medications, there are some side effects resulting from the use of indomethacin but in my experience proper regulation of dosage and proper observation of the patient has enabled the use of indomethacin without undue risk considering its beneficial effects.

Sincerely yours,

EMMERTON WARD, M.D.

ORTHOPEDIC AND ARTHRITIS CENTER,  
Oklahoma City, April 25, 1968.

Dr. MAX TISHLER,  
Merck Research Laboratories  
Merck & Co., Inc.,  
Rahway, N.J.

DEAR DOCTOR TISHLER: This letter is written regarding our work with indomethacin. We first began using this drug in 1961. At that time, a double blind study was carried out with indomethacin on patients with rheumatoid arthritis. It was directed by Dr. Richard Payne who is in charge of our drug evaluation studies. Recently, we have completed a study, again using the double blind technique on the use of indomethacin in patients with osteoarthritis. The results of the first study have been published (Payne, R. W.: Treatment of Rheumatoid Arthritis with Indomethacin, Jour. of Oklahoma State Medical Association, 553-537, December 1965). The results of the study on osteoarthritis have just been completed and the paper is now at the publishers.

The difficulty in evaluating drugs in the treatment of any form of arthritis is well recognized. We have felt that indomethacin is useful in a small but significant group of patients. This would be in the neighborhood of one patient out of four or five. The ones who fail to respond, of course, get no results but those who do respond may develop very desirable effects which, in some instances, would encourage a natural remission of the disorder.

If more details are needed regarding our work with indomethacin, please advise.

Sincerely yours,

WILLIAM K. ISHMAEL, M.D.

[Cable received in New York from São Paulo]

SÃO PAULO, April 25, 1968.

Mezey Reyour cable following are Dr. Cobra's statements addressed to Dr. Max Tishler quote in the light of my extensive experience in the management

of diseases for which indomethacin is indicated I have found that: indomethacin has highly contributed to the better management of our rheumatic patients, *sensu lato*, when administered within certain dosage limits, 25 to 75 milligrams orally per day or 100 mg. per day by rectal use. Above these limits there is a high increase in the incidences of side effects which limit the advantage in the use of the drug.

Indomethacin represents a valuable advance in the sense that it facilitated the compensation of certain chronic inflammatory syndromes and permitted the reduction of doses of other drugs such as phenylbutazone and steroids thereby reducing many of their side effects. Indomethacin alone; i.e., without being associated with other drugs or with other therapeutic measures does not seem useful to us because in most of the cases the necessary doses surpass the limits described above. Indomethacin has shown itself efficient as an Adjuvant E. "compensation" treatment of patients with rheumatoid arthritis ankylosing spondylitis and chronic gout arthritis as well as in the painful stage of osteoarthritis.

Summarizing: As a drug used alone indomethacin is efficient only in large doses but with a consequent high incidence of side effects. Indomethacin represents a drug of decisive efficacy when in moderated doses it is combined with other drugs.

Original statement being mailed today.

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[Cable received in New York from Mexico]

MEXICO, April 25, 1968.

DR. K. C. MEZEX, *Merck*:

Robles Gil reply as follows: 1 Since Indomethacin is drug that frequently allow treating patients in best way, 2 Indomethacin produces response in patient on whom previous treatment did not produce therapeutic response and permits the reduction of other drug such as corticosteroids. 3 Principal Indomethacin indication are rheumatoid arthritis. Degenerative articular problems gout. Memo follows.

IBARRA.

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THE UNITED NEWCASTLE UPON TYNE HOSPITALS,  
*Newcastle Upon Tyne, April 25, 1968.*

Dr. R. HODGKINSON,  
*Medical Unit,*  
*Merck Sharp & Dohme Limited,*  
*Hoddesdon, Hertfordshire.*

DEAR DR. HODGKINSON, I understand that the United States Senate is currently reviewing some aspects of the drug industry, including the status of Indomethacin. I have knowledge of articles published in non-medical journals, namely the Wall Street Journal and the Sunday Times, which have contained references to Indomethacin. In my opinion, these articles were inadequate and inaccurate in many aspects, as they failed to mention the properly conducted and controlled clinical trials which were done in 1962 and 1963, and which demonstrated the value of Indomethacin in the management of rheumatic disorders. In fact, Indomethacin was subjected to both the most prolonged and careful scrutiny that any drug had ever received prior to its introduction to clinical usage. Controlled trials and a considerable amount of subsequent clinical experience have fully justified the place of Indomethacin in Rheumatology.

I also feel that unjustifiable emphasis has been placed on side effects which are common to every drug used in medical practice, and in my opinion, the careful administration of Indomethacin constitutes one of the safest and most effective methods of drug treatment in the management of numerous rheumatic conditions. In particular Indomethacin is virtually exempt from the risk of haematopoietic, hepatic and renal side effects which complicate the use of many other drugs in rheumatology.

If you feel it would be helpful to produce this letter and the appended statement of my views on the usage of Indomethacin in rheumatology, you have my permission to do so.

Yours sincerely,

MALCOLM THOMPSON, M.D., M.R.C.P.,  
*Consultant Physician.*

Carefully controlled clinical trials have shown Indomethacin to be effective in the treatment of—

- Osteoarthritis
- Rheumatoid arthritis
- Ankylosing spondylitis
- Acute gout
- Capsulitis of shoulder
- Lumbar disk lesion with sciatica

In my experience, Indomethacin has either been the agent of choice or the only agent suitable on many occasions, in the treatment of the above listed conditions.

**Dr. LAWRSOHN.** In order to give the committee, Mr. Chairman, the benefit of the expert testimony of men who have thorough and extensive study of this drug, it is my pleasure to present to you first, Dr. John J. Calabro, who is associate professor of medicine at the University of California at Los Angeles School of Medicine and chief of the rheumatology section at Wadsworth Hospital, VA Center, in Los Angeles. It should be noted that Dr. Calabro has been, since 1963, the official representative to the National Society for Medical Research for the American Rheumatism Association.

**Senator NELSON.** We appreciate your coming here today, Doctor. Do you have a statement?

**STATEMENT OF JOHN J. CALABRO, M.D., ASSOCIATE PROFESSOR OF MEDICINE, DEPARTMENT OF MEDICINE, UCLA SCHOOL OF MEDICINE, CENTER FOR THE HEALTH SCIENCES; AND CHIEF, RHEUMATOLOGY SECTION, WADSWORTH HOSPITAL, VETERANS' ADMINISTRATION CENTER, LOS ANGELES, CALIF.**

**Dr. CALABRO.** I have a letter directed to you, Senator Nelson, and dated April 23.

I would like to begin first by submitting my credentials, my curriculum vitae. I am full-time associate professor of medicine at UCLA School of Medicine and, in that capacity, chief of the rheumatology section of an affiliated hospital, Wadsworth Hospital, VA Center, Los Angeles. I do not engage in the private practice of medicine. I am a full-time teacher and clinical investigator in the field of rheumatology.

(The curriculum vitae of Dr. Calabro follows:)

**CURRICULUM VITAE, JOHN JAMES CALABRO, M.D., MAY 1968**

**PRESENT POSITIONS (SINCE OCTOBER 1967)**

Chief, rheumatology section, Wadsworth Hospital, Veterans Administration Center, Los Angeles, Calif. 90073.

Associate professor of medicine, Department of Medicine, UCLA School of Medicine, Los Angeles, Calif. 90024

Born: Buffalo, New York—May 18, 1924.

Marital Status: Married—July 9, 1967—Mrs. Josephine (Puglisi) Calabro.

Medical Licensure: New York (75896) October 5, 1954, New Jersey (196498) June 4, 1958, California (G-14611) May 6, 1968.

Military Service: July 1944–June 1946 USNR, PhM 3/c.

Education: B.S., 1947, Canisius College, Buffalo, New York; Postgrad. Biology, September 1947–June 1948, Canisius College, Buffalo, New York; M.D., 1952, "cum laude" Georgetown University, School of Medicine, Washington, D.C.

Graduate Medical Education: Rotating intern, July 1952–June 1953, Mercy Hospital, Buffalo, New York; Junior Assistant Medical Resident, July 1953–June 1954, Georgetown University Hospital, Washington, D.C.; Senior Assistant

Medical Resident, July 1954-June 1955, Georgetown University, Washington, D.C.; Chief Medical Resident, July 1955-June 1956, Fourth (Harvard) Medical Service, Boston City Hospital, Boston, Massachusetts; Chief Medical Resident, July 1956-April 1957, Jersey City Medical Center, Jersey City 4, New Jersey; Visiting Clinical Fellow in Arthritis, April-June 1957, Hammersmith Hospital, London, England, Juvenile Rheumatism Unit, Taplow, England (under Prof. E. G. L. Bywaters); Clinical and Research Fellow, in Medicine (For study of Arthritis), July 1957-January 1959, Massachusetts General Hospital, Boston, Massachusetts.

Previous Academic Positions: Instructor in Biology, Sept. 1947-June 1948, Canisius College, Buffalo New York; Assistant in Medicine, July 1954-June 1955, Georgetown University School of Medicine, Washington, D.C.; Instructor in Bacteriology, July 1954-June 1955, Georgetown University School of Medicine, Washington, D.C.; Assistant in Medicine, July 1955-June 1956, Harvard Medical School, Boston, Massachusetts; Instructor in Medicine, July 1956-June 1957, Seton Hall College of Medicine, Jersey City 4, New Jersey; Visiting Fellow in Arthritis, April-June 1957, Postgraduate Medical School of London, London, England; Research Fellow in Medicine, July 1957-June 1958, Harvard Medical School, Boston, Massachusetts; Instructor in Medicine, July 1957-June 1958, (on leave of absence), Seton Hall College of Medicine, Jersey City, New Jersey; Assistant Professor of Medicine, July 1958-June 1962, Seton Hall College of Medicine, Jersey City, New Jersey; Associate Professor of Medicine, July 1962-October 1967, New Jersey College of Medicine (formerly Seton Hall College of Medicine), Jersey City, New Jersey.

Past Hospital Appointments: Director, Division of Rheumatology, July 1966 to October 1967, Veterans Administration Hospital, East Orange, New Jersey 07019; Assistant Attending Physician in Medicine for Rheumatic Diseases, January 1967 to October 1967, Newark City Hospital, Newark, New Jersey 07107; Assistant Attending Physician in Medicine for Rheumatology, April 1960 to October 1967, B. S. Pollak Hospital, Jersey City, New Jersey 07304; Attending Physician in Medicine, Chief, Arthritis Clinic, July 1958 to October 1967, Jersey City Medical Center, Jersey City, New Jersey 07304; Consultant in Rheumatology, April 1963 to October 1967 USPH Service Hospital, Staten Island, New York.

Scientific Societies: Diplomate, National Board of Medical Examiners, June 25, 1953; Certified, American Board of Internal Medicine, 1963; Fellow, American College of Physicians; Associate Fellow, American College of Cardiology; American Medical Association; Association of American Medical Colleges; American Association for the Advancement of Science; American Medical Writers' Association; American Heart Association; New York Academy of Sciences; American Rheumatism Association; Southern California Rheumatism Society; Horseshoe Club of England; The DiGamma Society of Canisius College.

Special Activities: American Rheumatism Association: Member, Education Committee, 1961-1962; Member, Committee on Exhibits, 1962-1963; 1964-present; Representative to National Society for Medical Research, 1963-present. The Arthritis Foundation: Delegate, Interchapter Medical & Scientific Committee, 1959-1967. National Association of Broadcasters Scientific Advisory Panel, Member, 1965 to present. Member, Editorial Board (Rheumatology Consultant), International Journal of Industrial Medicine and Surgery, 1967. Southern California Chapter, The Arthritis Foundation, Member, Medical and Scientific Committee, 1967; Chairman, Education Committee, 1967; Chairman, Post-graduate Seminar for SCGP Society, April 20, 1967.

#### Awards and Honors:

- (1) Canisius College, 1947: Graduation honor for excellence in philosophy.
- (2) New York State, 1947: War service scholarship.

- (3) Georgetown Medical School: Gold medals for highest academic standing in Bacteriology and Obstetrics & Gynecology. Honorable mention in Medicine, Oncology and Psychiatry. Cahill medal for highest academic standing in Surgery. Pediatric Thesis Award. C. V. Mosby Co. Award for highest academic standing in Senior Year.

- (4) The Arthritis Foundation, New Jersey Chapter, May 1967: The Robert Wood Johnson Humanitarian Award presented "For his dedication to the betterment of his fellow man and his devoted service to juvenile arthritis patients." This award is made annually to a native or resident of New Jersey who has made an outstanding contribution toward the better-

ment of his fellow man in the fields of medicine, social service or community activity.

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1959-1960: Wax moulage exhibit: "The feet in rheumatoid arthritis." Portrays clinical and radiologic features of feet of patients with rheumatoid arthritis, with special reference to heel and metatarsal lesions. (Calabro, J. J., Nosenzo, C. J., and Traugott, F.)

1960-1961: Wax moulage exhibit: "Arthritic feet." Utilizing the clinical and radiologic features of arthritic feet in the differential diagnosis of arthritis, including psoriatic arthropathy, rheumatoid arthritis, acute gouty arthritis, diabetic neuropathic joint disease and chronic tophaceous arthritis. (Calabro, J. J., Nosenzo, C. J., and Traugott, F.)

1961-1962: Ectochrome transparency exhibit: "Juvenile rheumatoid arthritis." Ectochrome illustrations demonstrating the protean manifestations of juvenile rheumatoid arthritis. (Calabro, J. J., Catsoulis, E., Nosenzo, C. J., and Traugott, F.)

1963-1964. Wax moulage exhibit: "The foot as an aid in the differential diagnosis of arthritis." (Calabro, J. J., Nosenzo, C. J., Luczynski, E., Jr., Abruzzo, J. L., Mody, R. E., and Traugott, F.) Award: AMA Honorable Mention.

1964-1965: Ectochrome transparency exhibit: "Tietze's Syndrome." (Calabro, J. J., Marchesano, J. M., Mody, R. E., Ruderman, J. E., Abruzzo, J. L., and Traugott, F.) Award: AMA Certificate of Merit.

Presentations of papers at national or international meetings:

June 2-6, 1959 (Washington, D.C.): Second Pan-American Congress on Rheumatic Diseases, in conjunction with the 23rd Annual Meeting of the American Rheumatism Association. Delivered paper on "The Feet in Rheumatoid Arthritis." Co-authored two other papers, one on "Some Observation on the Clinical, Chemical and Serologic Manifestations on Rheumatoid Arthritis. Based on a Study of the Course of 150 Cases," and "X-ray Examination of the Spine of Patients With Rheumatoid Arthritis and Spondylitis: A Correlation with Serologic and Clinical Manifestations of Disease."

September 4-7, 1961 (Rome, Italy): 10th International Congress of Rheumatology. Delivered paper on "The Foot as an Aid in the Differential Diagnosis of Arthritis."

September 13-15, 1962 (London, England): Salicylates: An International Symposium. Sponsored by the Empire Rheumatism Council, with the support of the Nicholas Research Institute, Ltd.: Held at the Post Graduate School of London. Discussor of therapeutic role of aspirin in rheumatoid arthritis.

June 13-14, 1963 (Atlantic City, New Jersey): Annual Meeting of the American Rheumatism Association. Co-chairman of arrangements. Delivered paper on "Observation on the Fever and Rash of Juvenile Rheumatoid Arthritis."

October 15-19, 1963 (Santiago, Chile): Third Pan-American Congress on Rheumatic Diseases. Delivered paper on "The Protean Manifestations of Juvenile Rheumatoid Arthritis."

October 1-3, 1964 (Princeton, New Jersey) : Conference on Gout and Purine Metabolism. Sponsored by the American Rheumatism Association, the National Institutes of Arthritis and Metabolic Diseases, and the Arthritis Foundation. Participant in clinical discussions.

June 17-18, 1965 (Philadelphia, Pa.) : Annual meeting of the American Rheumatism Association. Delivered paper on "Prognosis in Juvenile Rheumatoid Arthritis."

December 5-11, 1965 (Mar Del Plata, Argentina) : XIth International Congress of Rheumatology. Delivered paper on "Patterns of Onset and Course of Juvenile Rheumatoid Arthritis." Arthritis Foundation Travel Grant.

June 6-10, 1966 (New York, N.Y.) : Second International Symposium on Population Studies of the Rheumatic Diseases. Sponsored by NIH and the Arthritis Foundation. Secretary of the Council on Diagnostic Criteria for Juvenile Rheumatoid Arthritis. Member of Committee on Diagnostic Criteria for Ankylosing Spondylitis.

June 13-14, 1966 (New York, N.Y.) : International Conference on Chronic Administration of Salicylates. Sponsored by NIH and the Arthritis Foundation. Delivered paper on "Role of Salicylates in Juvenile Rheumatoid Arthritis."

June 16-17, 1966 (New York, N.Y.) : Annual Meeting of the American Rheumatism Association. Delivered paper on "Idiopathic Hypertrophic Osteoarthropathy (Pachydermoperiostosis) : Onset Before Puberty."

December 2-3, 1966 (Cincinnati, Ohio) : 12th Interim Scientific Session of the American Rheumatism Association. Delivered paper on "The Rash Associated With Juvenile Rheumatoid Arthritis."

June 15-16, 1967 (New York, N.Y.) : Annual Meeting of the American Rheumatism Association. Co-author of paper entitled "Rheumatoid Factor in Ankylosing Spondylitis." Chairman of one concurrent session.

Oct. 22-26, 1967 (Mexico City, Mexico) : IV Pan-American Congress of Rheumatology. Delivered two papers, one on "Indomethacin in Ankylosing Spondylitis," the other on "Prognosis in Ankylosing Spondylitis." Chairman of session on juvenile rheumatoid arthritis and Reiter's syndrome.

November 13-20, 1967 (Rome, Italy) : International Clinical Symposium, sponsored by Rome University in cooperation with the National Academy of Clinicians. Delivered several talks entitled "Situations in Rheumatology."

**Dr. CALABRO.** In my two-page letter dated April 23, I have summarized my experience and knowledge of the drug indomethacin and its role in patients with various rheumatic diseases.

My first comment pertains to recent reports of double-blind studies of indomethacin in rheumatoid arthritis. Conclusion of such studies have led to some controversy concerning the efficacy of this drug as an antirheumatic agent in patients with rheumatoid diseases. It is my opinion that, while double-blind studies are obviously useful in evaluating new agents, they are also extremely difficult to interpret, particularly in such a capricious disease—I am sure this has been stressed throughout the hearings—as rheumatoid arthritis. To this point, I might add—and I do not think this has been stressed—that there are few, if any, double-blind trials with other antirheumatic agents in rheumatic arthritis that are entirely satisfactory. These would include adrenocorticosteroids, gold compounds, antimarialials, phenylbutazone, and the well-known salicylates—drugs that are generally accepted in the care of rheumatoid patients.

Even controlled crossover techniques of drug testing can be faulty. In that regard, I would like to point to a publication that appeared in the Canadian Medical Association Journal on June 3, 1967. This is an article by a rheumatologist, T. D. Kinsella, and coworkers, MacKenzie, Kim, and Johnson. The title of this article, and I will submit this for the record, from the Journal of the Canadian Medical Association, is "Evaluation of Indomethacin by a Controlled, Crossover Technique in 30 Patients with Ankylosing Spondylitis."

(The document referred to follows:)

[From Canadian Medical Association Journal, vol. 6, June 3, 1967, pp. 1454-1459]

EVALUATION OF INDOMETHACIN BY A CONTROLLED, CROSS-OVER TECHNIQUE IN 30 PATIENTS WITH ANKYLOSING Spondylitis\*

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A clinical evaluation of indomethacin employing a controlled, cross-over technique with an inert placebo was undertaken in 30 patients with ankylosing spondylitis. Patients were studied for the frequency and dose relationship of side effects and for the subjective response of morning stiffness, chronic spinal pain, acute exacerbations of pain and peripheral arthralgia. Objective evaluation assessed measured change in movements of the cervical and lumbar spines, in chest expansion and in the range of movement of involved peripheral joints.

Evaluation of the results indicated that a significant number of patients experienced side effects in the form of headache and dizziness while receiving indomethacin in doses above 150 mg. per day. Many other side effects reported by the patients were not found to occur at a statistically significant level. The significance of pulmonary infections encountered in three patients was reviewed. Relief of chronic spinal pain and peripheral arthralgia occurred in 14 and 16 patients, respectively ( $p < 0.05$ ). Relief of morning stiffness and acute exacerbation of pain, and increase in the range of movement of any of the segments of the spine or the involved peripheral joints were not significant ( $p > 0.05$ ). Based on the results of this study, it is suggested that the role of idomethacin in the management of ankylosing spondylitis be re-evaluated and that the daily therapeutic dose of this drug which has been heretofore recommended be decreased.

Indomethacin is a non-steroid anti-inflammatory drug which has been reported to be of therapeutic value in a variety of rheumatic diseases.<sup>1-4</sup> Among the latter, ankylosing spondylitis has been reported to respond particularly well.<sup>5-7</sup> Because a large group of patients with ankylosing spondylitis previously studied<sup>8</sup> was available at Queen Mary Veterans' Hospital, a detailed controlled, crossover trial with indomethacin and a placebo was conducted on some of these patients to assess further the therapeutic efficacy of this agent.

MATERIALS AND METHODS

All patients in this study conformed to the criteria proposed by Kellgren<sup>9</sup> for the diagnosis of ankylosing spondylitis. Forty-eight patients were chosen at random as possible candidates; all of the latter were specifically advised of the side effects which were known to occur with indomethacin. Table I illustrates the eventual composition of the series. Only those patients who had clearly defined and persistent symptomatology were started on therapy. All patients were continued on their previous forms of medication, and these are indicated in Table II.

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NOTE.—Numbered footnotes at end of article, p. 3412.

TABLE I.—*Composition of study*

	Patients
Originally chosen for study	48
Started on medication	138
Lost to study:	
Failed to cooperate	5
Developed side effects	3
Completed study	30

<sup>1</sup> 10 omitted—Inability to cooperate or lack of consistent, well-defined symptoms.

TABLE II.—DISTRIBUTION OF TYPES OF MEDICATION EMPLOYED (OTHER THAN INDOMETHACIN) IN 30 PATIENTS WITH ANKYLOSING SPONDYLITIS

Type of medication	Daily dosage range (mg.)	Number of patients <sup>1</sup>
A.S.A. <sup>2</sup>	≥1,200	12
Phenylbutazone	>1,200	9
Steroids <sup>3</sup>	≥400	10
	>400	0
None	≤5	3
	>5	0
		5

<sup>1</sup> Total exceeds 30, since some patients employed more than 1 type of medication.

<sup>2</sup> A.S.A.=acetylsalicylic acid.

<sup>3</sup> Steroids expressed in equivalents of prednisone.

The range of the duration of illness in these patients was from 13 to 26 years, with a mean of 20.1 years. Capsules of indomethacin (25 mg.) and the placebo for oral use, and rectal suppositories of indomethacin (100 mg.) and the placebo were provided in identical forms. One suppository of the appropriate form was used at bedtime during the first six days of the first period of assessment. This procedure was not repeated during the second period of assessment, since it was felt that the patients would have become aware that substitution or "cross-over" had taken place. The dosage schedule for capsule therapy was 25 mg. twice a day for two days, then 25 mg. four times a day for two days, then 50 mg. three times a day for two days and then 50 mg. four times a day. Although indomethacin and placebo were assigned in a random manner, patients were advised to modify the daily dose, depending upon the occurrence and severity of the side effects experienced.

Reassessment was carried out by the same physician at three, six, nine and 12 weeks after the start of therapy. Cross-over to either indomethacin or placebo was carried out at the end of six weeks, but the assessing physician was not aware of which substance the patient had received. All medication was dispensed in the clinic by one physician who also assessed the frequency and severity of side effects, modification of the dosage schedule was recommended to the patients by this physician when it seemed appropriate. All medication which had not been consumed during each three-week period of assessment was returned by the patients to this physician, who then provided a further supply of a known amount of the appropriate medication.

Assessment of the therapeutic response was based upon both subjective and objective evaluation of the patients. The subjective evaluation was based on patients' opinions, which were graded as to whether the following showed "no change", were "worse" or "improved"; (a) duration and severity of morning stiffness, (b) severity of chronic pain in some or all segments of the vertebral column, (c) frequency and severity of acute exacerbations of pain, and (d) frequency and severity of peripheral arthralgia. Objective response was assessed by the following measurements: (1) movement in the cervical and lumbar spines as shown by the range of forward flexion and lateral flexion, extension and rotation, (2) maximal chest expansion, (3) degree of tenderness on "punch" palpation of the sacroiliac joints and (4) range of movement of the involved peripheral joints. The following criteria were employed to designate objective improvement: increase of at least 15° in each of two of the four basic movements in the cervical and lumbar spines, respectively; a sustained increase of at least one-half inch in chest expansion, improvement in the range of movement of two or more peripheral joints, or of at least 25% in a single peripheral joint.

Laboratory tests were done on each patient at each clinic visit in order to assess

both the side effects and the ability of indomethacin to suppress the various laboratory indices of inflammation. The following tests were performed routinely by conventional methods: complete urinalysis, complete hemogram including erythrocyte sedimentation rate (ESR-Wintrobe), blood urea nitrogen (BUN), serum creatinine, serum alkaline phosphatase, serum glutamic oxaloacetic transaminase (SGOT), serum protein paper electrophoresis, latex test for rheumatoid factor,<sup>10</sup> and antinuclear factor (ANF-LE-Test, Hyland). When indicated, chest film, barium meal, electrocardiogram, urine culture and antibiotic sensitivity (if any), and serum protein immunoelectrophoresis were also done. Statistical evaluation of the results was carried out by the chi-square test according to the method of McNemar, using one degree of freedom.<sup>11</sup>

TABLE III.—30 PATIENTS ON INDOMETHACIN AND PLACEBO: FREQUENCY OF SIDE EFFECTS

Type of side effect	Indomethacin		Placebo	
	Number	Percent	Number	Percent
<b>CNS:</b>				
Headache	15	50	7	23
Dizziness	12	40	3	10
Depression	2	6	1	3
"Feeling inebriated"	5	16	2	6
Miscellaneous	3	10	2	6
<b>Gastrointestinal:</b>				
Anorexia and nausea	7	23	7	23
Symptoms of peptic ulcer	11	36	9	30
<b>Skin eruption:</b>				
Skin eruption	3	10	0	0
Anemia	6	20	2	6
Elevated alkaline phosphatase	3	10	1	3
Elevated SGOT	1	3	1	3

<sup>1</sup> Significant at the 0.05 level.

<sup>2</sup> Decreased hearing, blurred vision and drowsiness—1 each.

## RESULTS

Twenty-seven patients completed six-week courses of both indomethacin and placebo, while one patient completed three-week courses of each. Two patients whose initial six-week course consisted of indomethacin and who experienced a severe clinical relapse during the first three weeks of placebo administration were subsequently restarted on indomethacin without the knowledge of the assessing physician. These 30 patients represent those who were assessed by the previously described clinical and laboratory parameters. Three additional patients who were lost to the study had received indomethacin only (Table I).

### Dose tolerated

The maximum daily dose of indomethacin tolerated without incapacitating side effects by 15 (50%) of the 30 patients was six capsules (150 mg.) per day, and by five others (16%) was four capsules (100 mg. per day). Thus, only 10 patients (34%) tolerated eight capsules (200 mg.) per day; in comparison to the placebo this was a highly significant difference ( $p=0.0015$ ).

### Side effects

Three patients who had received only indomethacin were forced to withdraw from the study (Table I). All of these patients experienced severe central nervous system reactions, principally headache and dizziness. One of these also developed extensive right middle and lower lobe pneumonitis which required hospitalization. The occurrence of a pulmonary infection was also noted in two other patients while they were receiving indomethacin.

Of the 30 patients who completed the study, 24 (80%) developed some form of side effect, as demonstrated either clinically or in the laboratory. Thus only six patients (20%) experienced no side effects while receiving indomethacin. On the other hand, 18 patients (60%) experienced some form of side effect while receiving placebo and 16 (53%) of the entire group experienced one or another of the side effects on both indomethacin and placebo. Viewed in this respect, there was no significant difference in the total number of side effects experienced on indomethacin or placebo ( $p > 0.05$ ).

The types and frequency of the various side effects are listed in Table III. It will be noted that reactions involving the central nervous system occurred with the greatest frequency, particularly those manifesting as headache and dizziness.

With respect to both of these symptoms there was a significant difference between the two treatment groups, the  $p$  values being 0.027 and 0.015 respectively. A similar difference was not found between the two treatment groups in regard to other complaints referable to the central nervous system, or indeed to any of the other side effects noted in Table III.

It should be noted that four patients whose gastrointestinal symptoms were severe were investigated by means of a barium meal, but in none of these patients was peptic ulceration demonstrated.

#### *Subjective response*

The results of subjective evaluation of the response to both drugs are depicted in Fig. 1. It will be seen that significant levels of response were noted with respect to relief of chronic spinal pain and peripheral arthralgia, the actual  $p$  values being 0.05 and 0.01, respectively. However, there was no significant difference in the responses of morning stiffness and of acute exacerbations of pain.

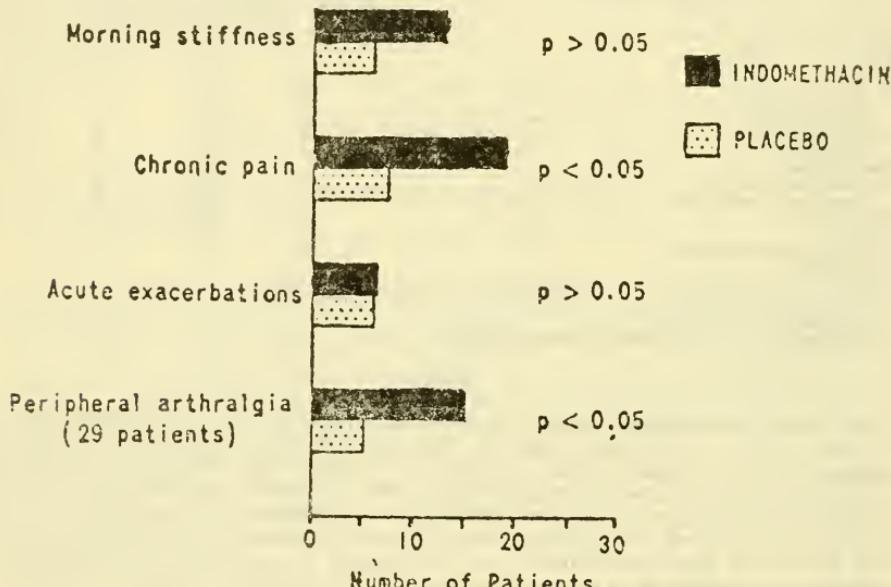


Fig. 1.—Subjective response to therapy in 30 patients with ankylosing spondylitis.

#### *Objective response*

Fig. 2 illustrates the results of objective evaluation of both drugs with respect to the cervical and lumbar spines, chest expansion, and sacroiliac and peripheral joints. It can be seen that in none of these parameters was there a significant difference between the two forms of therapy ( $p > 0.05$ ). Two additional findings should also be noted: first, the very small numbers of patients who demonstrated any subsequent variation in the measurements initially recorded; and second, the lack of correlation between the subjective and objective assessment of the peripheral joints.

TABLE IV.—EFFECT OF INDOMETHACIN AND PLACEBO ON LEVEL OF ESR AND ALPHA-2 GLOBULIN

	Number of patients	Decreased to normal by:	
		Indomethacin	Placebo
Elevated ESR-----	25	16 ( $p > 0.05$ )	2
Elevated alpha-2 globulin-----	26	18 ( $p > 0.05$ )	3

\* Significant at the 0.05 level.

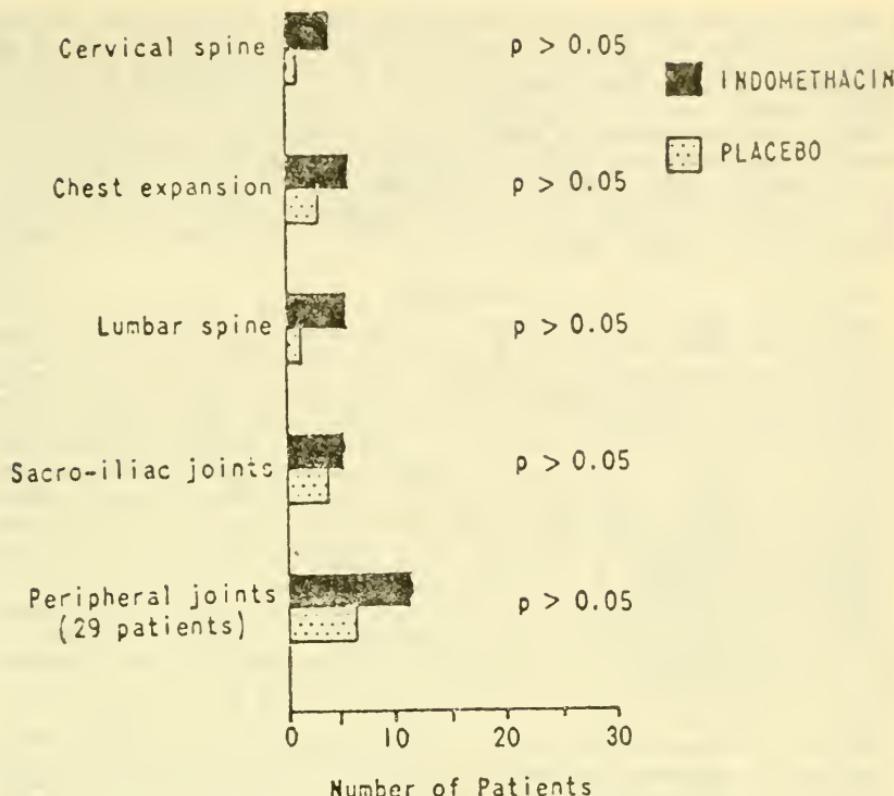


Fig. 2.—Objective response to therapy in 30 patients with ankylosing spondylitis.

#### *Laboratory results*

No abnormal results were encountered before or during both forms of treatment with respect to the serum antinucleoprotein test, latex fixation test, creatinine and BUN. Similarly, none of the patients exhibited a significant difference in the total white blood cell or differential counts on either drug. It should be noted that two of the three patients who developed a pulmonary infection were able to react with a neutrophilic leukocytosis (range: 11,000 to 21,000 per c.mm.) while the third showed no such response.

Abnormal urine was noted intermittently in eight patients (27%) while taking indomethacin and in 10 patients (33%) while taking a placebo; of the total of 18 patients there were four who had an abnormal urinalysis while receiving both indomethacin and placebo. Thus, 14 patients (47%) in this group showed abnormalities in the urinary sediment. These abnormalities were characterized by minimal proteinuria and microscopic pyuria and were usually not associated with dysuria. Their rate of occurrence could not be related to the administration of indomethacin ( $p > 0.05$ ).

The development of anemia (a fall of hemoglobin of greater than 1 g. %) was noted in six patients (20%) while receiving indomethacin and in two patients (6%) while receiving placebo (Table III): this was not significant at the 0.05 level ( $p > 0.05$ ). It should also be noted that an anemia of less than 13 g. % (range: 9-13 g. %) was present in six other patients before the administration of either drug and remained stable throughout the period of observation. Two patients who complained of symptoms suggestive of peptic ulcer also developed anemia. Investigation of these patients failed to demonstrate occult blood in the stool or, by barium meal examination, an upper gastro-intestinal tract ulceration.

Elevation of the ESR was found at some time during the study in 25 (83%) of the 30 patients, but in only eight, of whom six were receiving indomethacin and two placebo, did the ESR return to normal ( $p > 0.05$ ) (Table IV). By

serum protein electrophoresis the alpha-2 globulin was found elevated at some time during the study in 26 (86%) of the 30 patients; in the majority of patients the elevation was slight. The level of the alpha-2 globulin returned to normal values in eight patients (26%) while receiving indomethacin and in three patients (10%) while receiving placebo ( $p > 0.05$ ) (Table IV). Eight (26%) of the patients demonstrated a slight elevation of the serum gamma globulin on paper electrophoresis and none of these showed a significant change in this value during the period of observation. No significant difference at the 0.05 level ( $p > 0.05$ ) was noted with respect to the few patients who developed an abnormal elevation of the level of the serum alkaline phosphatase and glutamic oxaloacetic transaminase (Table III).

#### DISCUSSION

The relative value of any medication must be assessed with respect to potentially harmful side effects and the degree of both subjective and objective therapeutic benefits derived from it. The present study was undertaken to assess these factors as they applied to indomethacin in the treatment of ankylosing spondylitis.

In the majority of instances the rate of occurrence of side effects in the present group of patients with spondylitis was not shown to be significant by statistical analysis. It is probable that the many "placebo reactors" in this group resulted because the patients were specifically cautioned regarding these side effects at the onset of the study and because, during the course of the study, considerable attention was directed both to their occurrence and to their possible dose relationship. Accordingly, we do not feel that sufficiently unbiased data were obtained from this portion of the study to warrant extensive extrapolation.

Although the data were not shown to be statistically significant, note should be taken of the three patients who developed pulmonary infections while receiving indomethacin. In one patient, resolution occurred only after three weeks of antibiotic administration and withdrawal of indomethacin. In two of these patients a brisk leukocyte response was noted in the blood while in the third, the individual with the prolonged course who did not respond to antibiotics, no leukocytosis was detected. Since some experimental studies with indomethacin<sup>13</sup> do indicate an enhanced susceptibility to infection in animals the recent report by Phelps and McCarty<sup>14</sup> of decreased leukocyte mobility in the presence of indomethacin should prompt close re-evaluation of the incidence of infection in patients receiving this drug.

Abnormal urinalyses were noted intermittently in 14 patients (47%) during this study. Although apparent interference with normal renal function has been reported with indomethacin administration,<sup>14</sup> there was no statistical evidence in the present group of patients that the abnormal urinalyses were related to indomethacin therapy. Similar abnormalities have been previously reported by us<sup>8</sup> and are a recognized accompaniment of ankylosing spondylitis.<sup>15</sup>

The observations relating to the subjective and objective therapeutic responses to indomethacin provided more definitive data than those relating to the side effects. From the point of view of subjective evaluation, only the relief from chronic spinal pain and from peripheral arthralgia were found to be statistically significant responses. The failure of indomethacin to relieve morning stiffness in the spine and, in particular, to decrease the frequency and severity of acute exacerbations of spondylitis in this group of patients is in distinct contrast with the results reported in previous studies which did not employ a controlled, cross-over technique.<sup>6,7</sup> From the point of view of subjective response, therefore, indomethacin provided only minor benefit in the management of this group of spondylitis patients.

In none of the objective parameters of assessment was there a significant improvement with the administration of indomethacin. It should also be noted that the subjective improvement reported in peripheral arthralgia was not substantiated by objective assessment of the involved peripheral joints. These data clearly demonstrate the failure of indomethacin to produce objective improvement in the ranges of movement of the spinal and peripheral joints in this group of patients with ankylosing spondylitis.

It was considered possible that the very poor objective responses which were noted did not accurately reflect the anti-inflammatory potential of idomethacin, since, as has been previously indicated, the mean duration of illness in this group of patients was 20.1 years. In other words, it was possible that extensive immobilization of the vertebral column by ligamentous ossification and apophyseal joint fusion would prevent an objective display of improvement in the various ranges of movement. Accordingly, an attempt was made to reassess the data with

this possibility in mind by comparing the radiological changes in the vertebral column with the observed clinical responses.

As might be anticipated, it was virtually impossible to re-evaluate these data without introducing bias. The only definitive data which could be salvaged in this regard related to the cervical spine; employing the previously defined criteria for improvement, it was found that of 21 patients with no functionally significant radiological changes of ligamentous ossification and/or apophyseal joint fusion only one patient improved with indomethacin and none with placebo. On the other hand, of the remaining nine patients who were judged to have functionally significant radiological changes, three improved on indomethacin and one while on placebo. These observations would, therefore, suggest that the failure of these patients to demonstrate objective improvement was not due to mechanical restriction of the cervical spine but rather to failure of indomethacin to decrease or abolish active inflammation. It should also be noted that the latter conclusion is supported by the data which demonstrated the inability of indomethacin to prevent acute exacerbations and to relieve morning stiffness.

The laboratory tests (ESR and alpha-2 globulins) employed to assess the anti-inflammatory effect of indomethacin showed no significant change during this study. Once again these data correlate well with the other parameters used to assess indomethacin in this group of patients.

Although indomethacin has been reported to have both anti-inflammatory and analgesic properties,<sup>16-17</sup> the results of this study would indicate that on ankylosing spondylitis the main effect in indomethacin is as an analgesic, since the only significant responses observed were relief of chronic spinal pain and of peripheral arthralgia. The failure of indomethacin to decrease morning stiffness and the frequency and severity of acute exacerbations, to improve the restricted movements in the spinal and peripheral joints, or to suppress the elevated ESR and alpha-2 globulin levels would also indicate that the anti-inflammatory properties of indomethacin in chronic but active ankylosing spondylitis are minimal.

#### CONCLUSIONS

The majority of patients in this study were unable to tolerate the recommended daily therapeutic dose of up to 200 mg. per day of indomethacin. When 15 patients (50%) received a dose in excess of 150 mg. per day and five others (16%) a dose in excess of 100 mg. per day there was a high incidence of side effects. Accordingly, we would suggest that the maximum daily therapeutic dose of indomethacin be reduced below 150 mg. per day. It would also appear that if a beneficial therapeutic response does not occur with a dose between 100 mg. and 150 mg. per day, the probability that such a response will occur with higher doses is slight.

When the frequency and severity of indomethacin-related side effects, particularly those involving the central nervous system, are considered in conjunction with the apparent lack of an anti-inflammatory effect of indomethacin, the role of this agent in the routine management of ankylosing spondylitis should be questioned. Since in our experience<sup>8</sup> a satisfactory therapeutic program for ankylosing spondylitis can be achieved with physical measures, maintenance doses of acetylsalicylic acid and intermittent administration of phenylbutazone, we can discern no preferential role for indomethacin in such a program.

In order to further evaluate the role of indomethacin in the management of patients with ankylosing spondylitis, we would suggest that a cross-over study comparing phenylbutazone and indomethacin might provide more definitive data than were obtained in the present study. It would also seem appropriate to conduct such a study in a group of patients with spondylitis having a shorter duration of illness, so that objective assessment of the anti-inflammatory effects of the drugs would not be obscured by anatomically restrictive changes in the spine.

Appreciation is expressed to Dr. William Dorian of Merck Sharp & Dohme of Canada Limited, Montreal, for his generous support and encouragement, and to Dr. F. Robert MacDonald, Associate Radiologist at the Royal Victoria Hospital, Montreal, for his evaluation of the radiological examinations of this group of patients.

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- <sup>3</sup> Smyth, C. J., Velayos, E. E. and Amoroso, C.: Acta Rheum. Scand., 9 : 306, 1963.
- <sup>4</sup> Kelly, M.: J. Amer. Geriatr. Soc., 14 : 48, 1966.
- <sup>5</sup> Smyth, C. J. and Godfrey, R.: Arthritis Rheum., 7 : 345, 1964 (abstract).
- <sup>6</sup> Calabro, J. J. and Mody, R. E.: Bull. Rheum. Dis., 16 : 408, 1966.
- <sup>7</sup> Hart, F. D.: Brit. Med. J., 2 : 1281, 1965.
- <sup>8</sup> Kinsella, T. D., MacDonald, F. R. and Johnson, L. G.: Canad. Med. Ass. J., 95 : 1, 1966.
- <sup>9</sup> Kellgren, J. H.: Bull. Rheum. Dis., 13 : 291, 1962.
- <sup>10</sup> Singer, J. M. and Plotz, C. M.: Amer. J. Med., 21 : 888, 1956.
- <sup>11</sup> Maxwell, A. E.: Analyzing qualitative data, John Wiley & Sons Inc., New York, 1961, 26.
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- <sup>13</sup> Phelps, P. and McCarty, D. J.: Suppression of crystal-induced synovitis in canine joints by indomethacin: demonstration of inhibition of leukocytic motility. Paper presented at the annual meeting of the American Rheumatism Association, Denver, Colorado, June 17-18, 1966.
- <sup>14</sup> Wanka, J. et al.: Ann. Rheum. Dis., 23 : 218, 1964.
- <sup>15</sup> Copeman, W. S. C., editor: Textbook of the rheumatic diseases, 3rd ed., E. & S. Livingstone Ltd., Edinburgh, 1964, p. 526.
- <sup>16</sup> Sunshine, A. et al.: Clin. Pharmacol. Ther., 5 : 699, 1964.
- <sup>17</sup> Winter, C. A., Risley, E. A. and Nuss, G. W.: J. Pharmacol. Exp. Ther., 141 : 369, 1963.

Dr. CALABRO. This article requires comment, since rarely does any one study violate so many basic tenets of a drug evaluation. For instance, Senator Nelson, as part of the drug trial of indomethacin, all patients continued to take their previous medication, such as aspirin, phenylbutazone, or adrenocorticosteroids. In fact, some patients were even receiving two of these other drugs simultaneously.

Now, how do we test a drug if we allow patients to stay on another worthwhile and effective antirheumatic agent at the same time?

But even before undertaking the study—and this is an inherent difficulty of many crossover studies—unnecessary bias was introduced. All 30 patients, the investigators point out “were specifically advised of the side effects which were known to occur with indomethacin.”

In fact, the patients were so well advised that half developed indomethacin side effects while on placebo. In table III of their report, 60 percent of the patients had side effects—not ordinary side effects, but indomethacin side effects—while they were receiving placebo.

Predictably, such a poorly conceived and biased study produced inconclusive results. However, even more appalling—for me as a clinical rheumatologist responsible for the care of patients with rheumatoid spondylitis—even more appalling than their obvious errors of methodology are the apparent expectations by Kinsella and associates that indomethacin would provide “objective functional improvement.”

Now gentlemen, this is a clinical misconception, since antirheumatic agents are at best palliative. By providing effective relief of joint pain and inflammation, drugs then allow the clinician to utilize important supportive measures, such as therapeutic exercises and other forms of physical therapy.

To illustrate this point, Senator Nelson, if you had rheumatoid arthritis of the right wrist, and I were to give you an antirheumatic agent, be it corticosteroids or for that matter indomethacin, these drugs could relieve the inflammation and pain in your wrist joint. But if this effect required a number of weeks or a number of months, you would then end up with a joint that would have some restricted motion. No drug in the world is going to bring that motion back. The only measures that will correct this deformity, of course, are well-prescribed, regularly performed therapeutic exercises.

I might ask all of you gentlemen to analyze closely the double-blind studies reported by Dr. Mainland and more recently analyzed by Dr.

O'Brien, in order to question the role of so-called physical measures in these short-term studies. What about these physical modalities that I have just made reference to? Were such physical measures, as therapeutic exercises, standardized in the 11 clinics that were part of the cooperative clinic study of indomethacin? Actually, there was no mention of these in Dr. Mainland's paper. Again, you must realize that no drug will restore motion unless such impaired and limited joints are put through physical measures to increase ranges of motion, and this is obviously an important adjunctive part of the care of the rheumatoid patient.

I will stress again: Antirheumatic drugs do nothing more than remove joint pain and inflammation, and function is restored through supportive measures, such as physical therapy and so on.

Now, in spite of the results of the various double-blind and controlled trials that you have heard much testimony on, many physicians still have the impression that indomethacin benefits certain patients with rheumatoid arthritis. And, you have heard various statistics quoted, anywhere from 25 to 65 percent of rheumatoid patients may be benefited. But as Dr. Healey, a noted rheumatologist from Oregon, has pointed out in the Bulletin of Rheumatic Diseases in December 1967—there may be a subgroup of patients—be it small or large (whatever it is) who may be benefited by indomethacin, a finding that would certainly not be evident if all such patients are included in a general statistical evaluation. What is unique to those patients who do respond to indomethacin? And, to my knowledge, and I quote Dr. Healey, "This hypothesis has not been tested."

Earlier Senator Hatfield had asked about long-term evaluations of indomethacin in various rheumatic disorders. Dr. Charley Smyth, from Denver, Colo., will tell us shortly about his experience with indomethacin in rheumatoid arthritis. I have already submitted to you, Senator Nelson, a reprint of our long-term evaluation of indomethacin in ankylosing spondylitis. This is a form of rheumatoid disease affecting young men. It usually begins between ages 15 and 35. Unlike rheumatoid arthritis, it affects the small (apophyseal) joints of the back—but may also involve the peripheral joints, such as the knee and hip. In many ways, therefore, it is similar to rheumatoid arthritis.

In this indomethacin trial that I have submitted, averaging 33 months, and which is still continuing, actually into its seventh year, there were 28 ankylosing spondylitis patients who received an average daily dosage of 100 milligrams. The response to the drug—using three subjective criteria and three objective criteria, including the erythrocyte sedimentation rate (ESR) as follows: The overall therapeutic rating of all parameters proved to be good in 21 of 28 patients (75 percent), fair in five, and poor in two. (See table I.) Of the 28 patients, three of five patients who had previously been in functional class III improved to class II and two to class I; 21 patients eventually were in the most favorable functional class I, Senator, where only one patient was so rated before the start of indomethacin.

These functional designations are according to the scheme for long-term drug evaluations devised by the American Rheumatism Association, whereby functional class I means the patient is able to carry on all the usual activities of daily living and occupation, and class II means that he may be able to perform in these activities despite joint

limitation or handicaps. Class III means that the patient has difficulty maintaining self-care and occupation, while class IV refers to patients who are bedridden or confined to a wheelchair.

I would like to stress that I wish we had better measures for drug testing. While we have used this classification, and it is as effective as any we have today, it was devised in 1949. The Therapeutic Criteria Committee of the American Rheumatism Association are continuously devising techniques that might sharpen our therapeutic studies of new drugs even more.

I might add that in this study joint symptoms followed temporary withdrawal of the drug in 24 of the 28 patients—

Senator NELSON. You are talking about your study?

Dr. CALABRO. Yes, this has now appeared in the journal, Arthritis and Rheumatism, in February 1968.

Senator NELSON. Did you ask to have this printed in the record?

Dr. CALABRO. Yes.

Mr. CUTLER. It is attached to Dr. Calabro's letter.

Senator NELSON. It will be printed in the record at the conclusion of Dr. Calabro's statement.

Dr. CALABRO. Return of joint pain was then promptly relieved when indomethacin was again taken by the patients. Actually, we could repeat this withdrawal performance periodically.

Clearly, our report of indomethacin in spondylitis parallels the experience of others, such as Bilka from Minneapolis, Hart of London, and European investigators such as Koss and Pohl, and Rothermich, whom you heard yesterday, that indomethacin is effective in ankylosing spondylitis.

That indomethacin has antirheumatic effects in disorders other than ankylosing spondylitis is also apparent, as judged by numerous reports of its usefulness in the management of the majority of patients with gout—Dr. O'Brien puts it up to 80 percent of gout cases in his publication appearing in early 1968 (*Clinical Pharmacology and Therapeutics*)—and osteoarthritis of the hip.

I might refer to an additional followup publication, since Mr. Gordon has referred to the Katz, Pearson, and Kennedy article of January–February 1965 (*Clinical Pharmacology and Therapeutics*), but neglected to mention that at the end of that report it was clearly stated that these therapeutic trials were done with an outmoded indomethacin tablet that was never released. He also neglected to mention that Dr. Pearson, the senior investigator—and I would like to submit this also for the record—has since published on the indomethacin capsule, in May–June 1966, *Clinical Pharmacology and Therapeutics*, the same journal that Dr. O'Brien has his January–February 1968 publication in Pearson, having now used the capsule, has reported greater success in rheumatoid patients, but most notable was the reduction of adverse side effects, from 37 percent in their initial study to 12 percent in their continuation series, with no serious complications.

Finally, again, Mr. Gordon points to a poll on use of indomethacin in medical practice. We should mention very clearly that this is a poll on the treatment of rheumatoid arthritis. It is true that 8 percent of the pediatricians were using indomethacin. The comment is then made, "Unlike the internists, of whom over 50 percent were using indomethacin, this is in sharp contrast to the 310 pediatricians who relied pri-

marily on analgesics and combinations thereof, five out of 10, but only infrequently prescribed indomethacin, phenylbutazone, or gold.<sup>1</sup>

If you look even more critically at this report, you will note that 18 percent of pediatricians were using adrenocorticosteroids for the care of patients with juvenile rheumatoid arthritis. This is a most disturbing situation in young children, because steroids have many more hazards in the child than in the adult. For instance, it will suppress growth in height and weight. It may cause thinning of the bones, notably in the spine, which may then go on to vertebral fracture. Pseudotumor cerebri may also occur in children.

I have recently published all of the notable side effects of steroids that are unique to children. This data can be found in two parts, in the September 28 and October 5 issues of the *New England Journal of Medicine* in 1967.

We should also note that the pediatricians elected to use simple analgesics in half of their rheumatoid arthritis children. Accordingly, they are using agents that do not have the needed antirheumatic effect. How do they expect to get at joint inflammation with simple analgesics? How do they expect to restore joint motion without first alleviating joint pain and inflammation?

I sincerely hope, despite the current controversy and confusion, that investigative pursuits of indomethacin will continue. Only then can we more fully understand the role of this extremely useful and valuable antirheumatic agent. I have now been working with this agent—this is my seventh year. While I have only published reports of its usefulness in ankylosing spondylitis, I have used it in other disorders. Such data is certainly not scientifically organized and should not be presented, especially since none of it has been published. But I have also watched the growing literature on indomethacin very critically, and I have tried to present my estimation and fair appraisal of this most needed antirheumatic agent.

There are many conditions in the rheumatic disease field for which we have few agents. You may remember that yesterday, Mr. Gordon, we listed all of the agents we might use in rheumatoid arthritis. We listed, I think, five or six. For ankylosing spondylitis, a not uncommon disease, we can list only three agents. Besides indomethacin, there is phenylbutazone, which has its toxicity. The original report of phenylbutazone in spondylitis cited a 37-percent incidence of side effects.<sup>2</sup> X-ray therapy to the spine has now been generally abandoned because of the increased risk of leukemia. Court Brown, reporting in the *British Medical Journal* (2:1327-1332, 1965), cites 49 cases of chronic myelogenous leukemia due to radiotherapy. This has increased the hazard of leukemia from X-ray therapy in the spondylitis patient to some 10 times that of the population at large. Leukemia cases did not occur only after the forth, fifth, or sixth years after stopping radiotherapy, as we initially believed, but are occurring even now 14 and 15 years after radiotherapy was stopped.

I need indomethacin to treat my patients with ankylosing spondylitis, as indeed we need it for those patients with rheumatoid arthritis who do not respond to more conservative measures. Indeed, indo-

<sup>1</sup> See Toone, E. C., and Irby, W. R.: "Evaluation of Phenylbutazone (Butazolidin) in the Treatment of Rheumatoid Spondylitis: Report of 50 Cases." *Ann. Int. Med.*, 41: 70-78, 1954.

methacin is a valuable agent in the treatment of acute gouty attacks of arthritis, as it is in patients with osteoarthritis of the hip.

**Senator NELSON.** Thank you, Doctor. I think the testimony does not differ from what the FDA witnesses said yesterday about the use of indomethacin, except that you went into considerably more detail.

You suggested that the committee evaluate these tests. The committee does not feel competent to evaluate these tests. That is why we call in experts like you and who may well differ with each other. We feel that is the best way to find out what the truth is.

**Dr. CALABRO.** I hope I have made it apparent that most rheumatologists are unhappy about the methods we have for evaluating antirheumatic agents. As a matter of fact, Dr. Carl Pearson, professor of medicine at UCLA, as well as myself and three other investigators have just received an enormous grant aimed at the pharmacology and testing of drugs in arthritis. I am afraid to even mention the amount.

**Senator NELSON.** From where?

**Dr. CALABRO.** From the NIH, for \$3.5 million for 5 years. This grant was awarded Dr. Pearson to study the pharmacology of drugs—but more important, to ascertain newer techniques and tools by which we might better objectively evaluate current drugs, or newer drugs, used in the various rheumatic disorders. I hope that this represents at least the beginning of the type of support that many investigators will obviously need in order to evaluate the long term efficacy of antirheumatic drugs.

Clearly, we need a drug like indomethacin, and I hope to test indomethacin with our newer methods of objective evaluation as these become available.

**Senator NELSON.** Thank you very much, Doctor. We appreciate your coming to testify today.

(The letter and supplemental information submitted by Dr. Calabro follow:)

APRIL 23, 1968.

Hon. GAYLORD NELSON,  
*Chairman, Subcommittee on Monopoly, Senate Committee on Small Business,  
U.S. Senate, Washington, D.C.*

DEAR SENATOR NELSON: In anticipation of my participation in the congressional hearing of your committee on May 3, 1968, the following summarizes my experience with the drug indomethacin and the role it has in the management of patients with rheumatic diseases.

Recent reports of double-blind studies of indomethacin in rheumatoid arthritis (RA) have caused considerable controversy concerning the efficacy of this drug as an antirheumatic agent. It is my opinion that while double-blind studies are obviously useful in evaluating new agents, they are also extremely difficult, particularly in such a capricious disease as RA. To this point, I might add that there are few (if any) double-blind trials with other antirheumatic agents that are entirely satisfactory.

Even more appalling are the apparent expectations of many investigators conducting short-term studies in RA that indomethacin would provide objective functional improvement. This is a clinical misconception since all antirheumatic agents are at best palliative. By providing effective relief of joint pain and inflammation, rugs allow patients to undertake therapeutic exercise and other supportive measures. These provide objective improvement. Yet, such measures receive scant mention and do not appear to be an integral part of the reported double-blind studies of indomethacin in RA.

In spite of these controlled trials, many physicians have the impression that indomethacin benefits certain patients with RA. As Healey has recently pointed out in the Bulletin of the Rheumatic Diseases (18, 483, 1967), there may be a sub-group of patients with RA that are controlled by indomethacin, a finding that

would not be evident when such patients are included in a general drug trial. To my knowledge, this hypothesis has not been tested.

The result of our long-term evaluation of indomethacin in ankylosing spondylitis (AS), a form of rheumatoid disease affecting young men, has recently appeared in the journal *Arthritis and Rheumatism* (11:56, 1968).

In this trial of indomethacin averaging 33 months in 28 AS patients who received an average daily dosage of 100 mg., the response to the drug was good in 21 patients, fair in 5 and poor in 2. Of the 28 patients, 21 improved to ARA functional class I. Before the use of indomethacin, only one of the 28 was so rated. Joint symptoms followed temporary withdrawal of the drug in all but four of the 28 patients. These symptoms were promptly relieved when indomethacin was again taken by the patients.

Clearly, our report parallels the experience of others, such as Bilka, Hart, Kass, Pohl, Rothermich and De Seze, that indomethacin is an essentially safe and effective drug in suppressing the articular manifestations of AS.

That indomethacin has antirheumatic effects in disorders other than AS is also apparent, as judged by numerous reports of its usefulness in the management of the majority of patients with gout and osteoarthritis of the hip.

I sincerely hope, despite the current controversy and confusion, that investigative pursuits of indomethacin will continue. Only then can we more fully understand the role of this extremely useful and valuable antirheumatic agent.

Best wishes,

Very truly yours,

JOHN J. CALABRO, M. D.,

*Chief, Rheumatology Section, Wadsworth Hospital,  
Associate Professor of Medicine, UCLA School of Medicine.*

[From *Arthritis and Rheumatism*, vol. 11, No. 1 (February 1968), pp. 56-64]

#### INDOMETHACIN IN ANKYLOSING SPONDYLITIS

(By John J. Calabro and Clemente M. Amante)

(From the Division of Rheumatology, Department of Medicine, New Jersey College of Medicine.)

Supported in part by Grant 2A-5148 from the National Institutes of Health, United States Public Health Service.

John J. Calabro, M.D. F.A.C.P.: Formerly Associate Professor of Medicine and Director, Division of Rheumatology, New Jersey College of Medicine, Medical Center, Jersey City. Currently Associate Professor of Medicine, UCLA School of Medicine, and Chief, Rheumatology Section, Wadsworth Hospital, VA Center, Los Angeles, Calif. 90073. Clemente M. Amante, M.D.: Fellow in Medicine, New Jersey College of Medicine, Medical Center, Jersey City.)

Among the more promising newer drugs used in the treatment of rheumatic diseases, indomethacin occupies an important place. This nonsteroidal anti-inflammatory indole compound became available for clinical trials in November, 1961. Studies since then have variously evaluated its potential effectiveness in rheumatoid arthritis<sup>1-9</sup> Reiter's disease,<sup>1-3</sup> psoriatic arthritis,<sup>1-3-9</sup> ankylosing spondylitis,<sup>1-5-10-12</sup> gout,<sup>1-3-3-4</sup> rheumatic fever<sup>13</sup> and degenerative joint disease.<sup>1-4-6-10</sup>

A number of studies<sup>1-4</sup> have pointed out that the best results with indomethacin were obtained with low dosages, and that even then, the incidence of side effects, such as dizziness, headaches and gastrointestinal disturbance, was unfortunately high. Rothermich<sup>1-17</sup> has recently shown that even using dosages as low as 25 mg. daily, the physician must be on guard for the occasional patient who may develop gastric upset or even ulceration, or the unusual patient who is highly susceptible to cerebral side effects.

It is well established now that with indomethacin, as with all antirheumatic drugs, dose-related side effects may appear either early in treatment or when the drug is taken over a long period of time.<sup>3-17</sup>

While our early experience with the drug yielded extremely variable results in peripheral rheumatoid arthritis, far more predictable and satisfactory disease suppression was noted in ankylosing spondylitis (AS). Since then, and after reporting some preliminary results,<sup>18</sup> we have maintained 28 AS patients on indo-

methacin in a clinical study that is now in its fifth year. A battery of laboratory tests was done before and periodically during this drug trial. Thus, we were able to combine a long-term therapeutic evaluation of indomethacin with a continuous monitoring of possible side effects.

#### MATERIALS AND METHODS

*The patient group.* Only patients with active AS were selected for this study. They were 25 men and 3 women who attend the arthritis clinics of the Jersey City Medical Center. They have been treated with indomethacin for periods ranging from 5 to 52 months, or for an average of 33 months (Table 1). On analysis in April, 1967, the age of the patients averaged 41 years, ranging from 20 to 58 years. The duration of disease averaged 19 years, ranging from 3 to as long as 36 years.

The mean age of the patients at disease onset was 24 years. The longest interval between onset and diagnosis was 25 years in one man, but the average interval proved to be 9 years. The mode of onset was insidious in 18 patients and acute in 10. Initial involvement was found to be axial (spinal) in 14 patients, peripheral in 13 and systemic (with recurrent iritis) in one. Of 14 patients with axial onset, 12 had lumbar, one had dorsal, and one had cervical involvement. Of the 13 patients with AS of peripheral onset, 6 had involvement of the hip, 4 of the knee, 2 of the shoulder, and one of the heel.

Serial x-rays have disclosed bilateral sacroiliitis, apophyseal irregularities, and some degree of vertebral demineralization or squaring in all 28 patients. Three patients have associated ulcerative colitis and two have regional enteritis.

Major systemic manifestations in these 28 patients before the indomethacin trial included iritis in 6 patients, aortic insufficiency in 2, angina in 2, while one patient each had vasculitis and cauda equina involvement (Table 2). Persistent EKG abnormalities, chiefly in the form of conduction disturbances, were noted in 10 patients.

Prior to the trial with indomethacin, one patient was in functional class I, 21 in class II, 5 in class III, and one in class IV (Table 1).<sup>19</sup> Previously of the 28 patients, 15 had taken aspirin (daily dosage 1.5 to 6.0 Gm.), 9 had received phenylbutazone (100 to 300 mg.), one oxyphenbutazone (300 mg.), while 3 had taken various types and amounts of adrenocorticosteroids.

*Indomethacin dosage.* The initial dosage of indomethacin administered to each patient was 100 mg. daily, with 25 mg. capsules given after meals and at bedtime. Daily maintenance dosages were then adjusted to the lowest possible required for individual suppression of active articular disease. Adjunctive measures, such as physical therapy, were encouraged. But no medication other than the test drug was administered except in one patient who was gradually being weaned from adrenocorticosteroids.

*The study design.* Each patient was evaluated initially, and again at weeks two, six and 12, and then at three-month intervals. At the initial visit, a detailed work-up, including history, physical examination, x-rays, electrocardiogram and a battery of laboratory studies, was performed on each patient. The patient's functional status was then assessed by means of the ARA Steinbrocker criteria.<sup>19</sup>

At each follow-up visit, careful histories were taken and physical examinations were performed on all patients.

In addition four parameters of disease activity were selected for initial and continued assessment. The parameters were: 1) joint pain, 2) duration of morning stiffness, 3) onset of fatigue and 4) joint mobility including spine extension and flexion chest cage expansion and range of motion of peripheral joints.

To serve as a control phase, temporary withdrawal of indomethacin was carried out in all patients after they had been maintained on the drug for a period of at least three months. The drug was promptly readministered once active disease had recurred.

Laboratory studies performed before indomethacin administration and each time we saw the patients included serum SGOT, SGPT, alkaline phosphatase, cephalin flocculation, thymol turbidity, total bilirubin, total protein and A/G ratio, BUN, uric acid, paper electrophoresis, latex fixation and blood glucose. Of the last 8 patients admitted to the trial, serum studies included only a BUN, SGOT, uric acid, paper electrophoresis and latex fixation test.

Other studies performed initially and on each follow-up visit on all 28 patients included a Westergren ESR, hematocrit, WBC and differential counts, urinalysis and a stool guaiac test.

At follow-up, patients were asked to report any adverse reactions to the drug. Upper G-I series were performed on only those patients who had gastrointestinal complaints. X-rays of axial and involved peripheral joints and electrocardiograms were performed yearly. An ophthalmologic evaluation including slit lamp examination was conducted on all 25 patients who had received indomethacin for more than one year.

*Evaluation of findings.* Therapeutic assessments done at the end of the trial consisted of evaluation of: 1) ARA functional class, 2) the four selected parameters, singly and collectively, 3) calculation of average maintenance dosage, 4) the withdrawal phase of the trial, 5) ESR values, 6) systemic manifestations, and 7) adverse reactions to the drug.

The four selected parameters were rated as improved when joint pain decreased in intensity, duration of morning stiffness diminished by at least one-half hour, onset of fatigue decreased by at least two hours, and the total range of joint motion increased by 25 per cent or more.

We also devised an over-all therapeutic rating scale, whereby improvement in three or four of these selected parameters was graded as good, in one or two as fair, and in none as poor.

TABLE I.—CLASSIFICATION OF THE 28 PATIENTS AND RESULTS OF INDOMETHACIN TRIAL

Pt. No.	Sex	Age	AS onset (yr.)	Indomethacin Daily main-tenance (mg.)	Functional class <sup>1</sup>		ESR		Individual improvement <sup>2</sup> in		Overall response <sup>3</sup>	Side effects and month first noted	
					Before Rx	Length of Rx (mo.)	Before Rx	After Rx	Joint pain	AM stiffness	Onset of fatigue		
(1)	F	53	25	100	39	111	=	98	18	+	+++	Good	
(2)	M	39	15	100	20	111	35	54	++	-	++	do	
(3)	M	45	30	75	20	111	100	71	++	-	++	do	
(4)	M	42	24	100	18	111	98	47	++	-	++	do	
(5)	M	27	14	100	39	111	34	15	++	-	++	Nausea, 2d month; dizziness, 2d month.	
(6)	M	46	40	100	40	111	5	15	++	-	++	do	
(7)	M	53	33	75	51	111	35	1	++	-	++	Fair	
(8)	M	58	30	125	41	111	23	7	+	-	+	Good	Headache, 6th month; nausea, 29th month; diarrhea, 24th month.
(9)	M	51	17	200	51	111	67	7	+	-	+	do	Headache, 24th month.
(10)	M	49	14	25	45	111	-	61	28	+	-	Fair	Headache, 2d month.
(11)	F	23	14	200	27	111	-	3	6	++	++	Good	
(12)	M	58	32	100	17	111	-	4	9	++	++	do	Dizziness, 2d month.
(13)	M	48	40	100	18	111	-	37	10	++	++	Fair	
(14)	M	44	24	100	50	111	-	33	32	++	++	Good	
(15)	M	30	16	100	29	111	-	15	15	++	++	Fair	Nausea, 22d month; diarrhea, 22d month.
(16)	M	21	18	200	49	111	-	20	4	++	++	Good	
(17)	M	36	17	100	38	111	-	22	5	++	++	do	Nausea, 3d month; headache, 3d month.
(18)	M	43	22	200	52	111	-	27	15	++	++	do	
(19)	M	32	21	100	40	111	-	10	12	++	++	do	
(20)	M	40	20	150	39	111	-	30	2	++	++	do	
(21)	M	20	14	75	52	111	-	42	44	++	++	Fair	
(22)	M	47	26	125	21	111	-	37	53	++	++	Good	
(23)	M	44	20	100	38	111	-	20	21	++	++	do	
(24)	M	22	18	100	21	111	-	2	1	++	++	Poor	
(25)	M	55	25	100	6	111	-	102	82	-	-	Good	
(26)	M	31	25	50	40	111	-	5	3	++	++	do	
(27)	F	53	23	100	6	111	-	105	105	++	++	Poor	
(28)	M	39	36	75	5	111	-	11	11	-	-	do	Nausea, 1st month.
Average		41	24	100	33	111	-	39	26	-	22	17	17
Total		(6)			(7)			(8)	25	-	-	(9)	11 months (range 1 to 34 months). 13 side effects (8 pts.).

<sup>1</sup> American Rheumatism Association classification: Class I—Ability to carry on a usual duties without handicaps. Class II—Adequate for normal activities despite handicap or limited motion of 1 or more joints. Class III—Limited only to little or none of duties of usual occupation or self-care. Class IV—Bedridden or confined to wheelchair; little or no self-care.

<sup>2</sup> The 4 selected parameters were rated as improved when joint pain decreased in intensity during a morning stiffness diminished by at least  $\frac{1}{2}$  hour, onset of fatigue decreased by at least 2 hours, and the degree of joint mobility increased by 30 percent or more.

<sup>3</sup> Overall therapeutic rating scale, whereby improvement in 3 or 4 of the selected parameters were graded as good, in 1 or 2 as fair, and in none as poor.

<sup>4</sup> This woman, with a 15-year history of diabetes, died following a second episode of myocardial infarction. No autopsy was obtained.

<sup>5</sup> The "p" value obtained from Student's "t" test is statistically significant at the <0.01 level after testing the average paired differences against zero for the ESR values before and after indomethacin.

<sup>6</sup> Total: Male, 25; female, 3.

<sup>7</sup> Total by classification: Class I, 21; class II, 5; class III, 6; class IV, 1.

<sup>8</sup> Total by classification: Class I, 21; class II, 6; class III, 0; class IV, 1.

<sup>9</sup> Total: Good, 21; fair, 5; poor, 2.

TABLE 2.—SYSTEMIC MANIFESTATIONS OF ANKYLOSING SPONDYLITIS DEVELOPING DURING INDOMETHACIN TRIAL AVERAGING 33 MONTHS

Systemic manifestations	Number of cases before indomethacin trial	Number of cases during indomethacin trial
Iritis	16	3
Angina pectoris	2	0
EKG conduction changes	10	4
Aortic insufficiency	2	1
Foot and ankle ulcerations	0	1
Vasculitis	1	0
Cauda equina lesion	1	0
Total	22	9

<sup>1</sup> 1 patient had 3 bouts of iritis during the indomethacin trial, but had had recurrent iritis before this trial while receiving other antirheumatic agents. Two other patients experienced their first bouts of iritis while receiving indomethacin.

## RESULTS

Indomethacin proved an effective suppressive agent of the articular manifestations of AS in the present study, as judged by the following:

1. After treatment for an average period of 33 months, 21 of our 28 patients were in the most favorable functional class I,<sup>10</sup> as compared with only one of 28 before utilization of indomethacin (Table 1). Of 5 patients in functional class III before the drug trial, 3 improved to class II, and 2 to class I.

2. Analysis of each of the four selected parameters revealed a decrease in joint pain in 25 of 28 patients (89 per cent), a decrease in the duration of morning stiffness in 22 (79 per cent), delay in the onset of fatigue in 17 (61 per cent), and an increase in joint mobility in 17 patients (61 per cent) (Table 1). Joint pain and morning stiffness diminished promptly after indomethacin was started, usually in 48 hours, or within one to 7 days. Alleviation of fatigue and improvement in joint mobility was less dramatic, taking from one week to 3 months, and occurring on the average within 4 weeks.

After an average treatment period of 33 months with indomethacin, the over-all therapeutic rating of all four parameters was good in 21 of 28 patients (75 per cent), fair in 5 (18 per cent) and poor in 2 (7 per cent) (Table 1).

3. The average daily maintenance of indomethacin required for suppression of articular disease was 100 mg., the lowest was 25 mg. and the highest 200 mg. (Table 1). Only 7 patients needed more than 100 mg. daily, 5 with active hip or other peripheral joint disease, 2 because of marked axial (spinal) involvement.

4. When indomethacin was withdrawn, severe axial pain and morning stiffness recurred on an average within 48 hours in 24 of the 28 patients. Symptoms were promptly alleviated in all 24 patients when indomethacin was readministered.

Of the remaining four patients, two (Table 1, patients no. 25 and 28) did not respond to the drug and therefore exhibited no symptoms when indomethacin was withdrawn. Two patients (patients no. 15 and 17) had achieved remission.

5. The average Westergren ESR values for all 28 patients decreased during the drug trial from 39 mm. to 26 mm. (Table 1). The *p* value obtained from Student's *t* table is statistically significant at the <0.01 level after testing the average paired differences against zero for the ESR values before and after indomethacin.

ESR values were normal (15 mm. or less) initially and remained so in 8 patients (29 per cent). Eight other patients (29 per cent) attained normal ESR values by the end of the trial. Thus, normal ESR values were noted in 16 patients (58 per cent) while on indomethacin (Table 1).

Only 4 patients had marked ESR values after the trial. Response to indomethacin was good in 2 patients, fair in one and poor in one (Table 1).

6. While articular manifestations of AS were generally controlled with indomethacin, certain systemic manifestations of the disease were not (Table 2). During long-term maintenance on indomethacin, iritis occurred in 3 patients, and multiple recurrent ulcerations of the left foot and ankle in one patient. The murmur of aortic insufficiency developed in one patient, while EKG conduction disturbances developed in 4 patients. Cauda equina involvement of three years' duration in one patient, manifested by nocturnal incontinence, poor stream and diminished bladder and rectal sensation, did not improve with indomethacin.

Despite suppression of articular symptoms in all but two of the 28 patients, serial x-rays of axial and involved peripheral joints disclosed progressive changes in the majority of patients.

7. A total of 13 side effects, often transient and usually observed during latter months of indomethacin administration, occurred in 8 patients on maintenance dosages of 25 to 200 mg. daily (Table 1). Each of the 4 patients receiving the daily maximum of 200 mg. had adverse reactions.

Headache was noted in 4 of the 8 patients. Of the 4 patients with headache, one also had nausea, and another nausea and diarrhea. Two patients had dizziness, one of whom also had nausea. Two other patients had nausea, one of whom also had diarrhea.

All side effects disappeared spontaneously even though the drug was continued at the same dosage, except for 2 patients whose symptoms persisted until the daily maintenance of indomethacin (200 mg.) was temporarily reduced. Side effects did not reoccur in these 2 patients when 200 mg. dosages of indomethacin were reinstated at a later date.

Upper GI series, performed on the 5 patients with gastrointestinal side effects, revealed no abnormalities. Overt gastrointestinal bleeding did not occur, despite the intermittent presence of positive stool guaiac tests in 6 patients.

There was no evidence of any ocular, renal, hepatic or hematopoietic side effects. There appeared to be no increased susceptibility to infection.

Indomethacin was discontinued in three patients. It was withdrawn in one patient (patient no. 25) with regional enteritis and active foot and heel involvement because his response to indomethacin was poor, after having been tried on three different occasions over a six-month period. It was discontinued in another patient (patient no. 28) because of a poor response after 5 months on the drug. Both patients have been more adequately controlled with 300 mg. phenylbutazone daily.

Indomethacin was temporarily discontinued in a man with associated ulcerative colitis (patient no. 18) when the patient developed multiple recurrent ulcerations of the left foot and ankle after he had taken 200 mg. of the drug daily for 36 months. But indomethacin was resumed three months later after two biopsies of the lesion proved negative for vasculitis. The ulcer has now healed.

#### DISCUSSION

Our most striking observation about indomethacin is the clear-cut benefit it seems to provide in ankylosing spondylitis.

When indomethacin is used in other rheumatic disorders, such as rheumatoid arthritis, psoriatic arthritis, Reiter's syndrome or juvenile rheumatoid arthritis, one cannot predict if a patient will benefit from its use.<sup>1,4,10-12</sup>

But as demonstrated in this study, and as suggested by other reports,<sup>1,3,4,6,9</sup> indomethacin seems to be almost consistently effective in ankylosing spondylitis. Despite this enthusiasm about indomethacin, it must be kept in mind that this drug, like other antirheumatic agents, does not specifically alter the underlying disease process. Thus, while articular manifestations of ankylosing spondylitis are suppressed with indomethacin, systemic features appear not to be affected.

The disease activity of most rheumatic disorders is usually reflected in the erythrocyte sedimentation rate (ESR), but this relationship does not seem to be as precise in ankylosing spondylitis as in rheumatoid arthritis.<sup>20</sup> A possible correlation between disease activity and the ESR was suggested in this study, when more than half or 16 of the 28 patients either maintained or achieved a normal ESR value paralleling a favorable therapeutic response. This finding has not been reported previously.

In most cases, ankylosing spondylitis tends to be relatively stable for long periods, so that the symptomatic effects of a single drug can be evaluated by using the patient as his own control. Consequently, when indomethacin was temporarily withdrawn, articular manifestations usually recurred within 48 hours, and were then promptly alleviated when indomethacin was resumed. Therefore, we agree with Kass<sup>11</sup> that it is not necessary to utilize complicated therapeutic experiments in a disease such as ankylosing spondylitis. But, since we did not use a double-blind crossover approach, including a placebo and other antirheumatic agents, we cannot report any objective comparisons between indomethacin and other drugs useful in AS. Furthermore, we were convinced at the beginning of this study that the long-term administration of a placebo to patients with active disease and its attendant distress and discomfort cannot be justified ethi-

cially. Wallace and Ragan<sup>21</sup> had similar convictions about the use of placebo in patients with active rheumatoid arthritis.

Despite the fact that the world literature now abounds with warnings of the potential side effects of even small doses of indomethacin, none of our 28 patients were forced to discontinue the drug because of side effects. Indomethacin was stopped in 3 patients, in 2 because of a poor therapeutic response, and in the other only temporarily, when he developed infected foot and ankle ulcerations which proved later not to be due to the drug.

Nevertheless, our findings support the view that side effects are most frequent among patients receiving larger amounts of the drug,<sup>14</sup> while they are also in agreement with the concept, stressed by Rothermich,<sup>17</sup> that cerebral side effects may occur on low dosages in susceptible individuals. All 4 patients on the highest daily indomethacin maintenance dosage of 200 mg. experienced adverse reactions to the drug, while 4 other patients receiving small daily dosages of 25 to 100 mg. developed headache and dizziness. Most drug reactions disappeared spontaneously, except in 2 patients whose side effects persisted until the dosage of indomethacin was reduced.

The rather late occurrence of most side effects, though briefly mentioned elsewhere,<sup>3, 17</sup> has not been stressed prior to this investigation. Annoying headache or gastrointestinal upset were not seen soon after patients were started on indomethacin. In fact, the 13 side effects observed in 8 of our 28 patients usually occurred only after months and even a year or more of indomethacin administration. In any case, close attention to minimal individualized dosages needed for disease suppression appears to reduce the occurrence of potential side effects. This has also been the experience of Boardman and Hart.<sup>22</sup>

In conclusion, despite the fact that indomethacin has been found of considerable therapeutic usefulness, we do not mean to give the impression that we are treating patients merely with drugs. On the contrary, we cannot emphasize sufficiently the overriding importance of treating the entire disease, particularly with physical, recreational and rehabilitative measures. All of these are intrinsic parts of the overall management of the patient with ankylosing spondylitis.<sup>18</sup>

#### ACKNOWLEDGMENTS

We are indebted to Dr. Rustom E. Mody, former Fellow in Rheumatology, for his early assistance in this study to Dr. Bertram W. Charap of the Mt. Sinai Hospital in New York City for ophthalmologic studies and to Mr. John Wykert of Science & Medicine Publishing Co., Inc., New York, for his assistance in the preparation of this manuscript.

The indomethacin used in this study was supplied by Dr. Nelson H. Reavey Cantwell of Merck Sharp and Dohme, Research Laboratory, West Point, Pennsylvania.

#### SUMMARY

Indomethacin was found to be highly effective in the management of 28 patients with ankylosing spondylitis in a clinical trial that is now in its fifth year. As judged by selected criteria, including joint pain, duration of morning stiffness, onset of fatigue and joint mobility, the response to the drug was good in 21 patients, fair in 5 and poor in 2. After receiving indomethacin for an average period of 33 months, 21 of the 28 patients were classified in ARA functional class I. Only one patient had been so classified prior to the drug trial. Joint symptoms followed temporary withdrawal of the drug, but were promptly relieved when indomethacin was again taken by the patients. However, while articular manifestations of ankylosing spondylitis were suppressed by indomethacin, systemic features were not.

Therapeutic maintenance doses of indomethacin were carefully individualized. While the average daily dosage proved to be 100 mg., four patients with marked peripheral and axial joint involvement required 200 mg. daily.

A battery of laboratory tests accompanied the entire period of the drug trial. These tests revealed no ocular, renal, hepatic or hematopoietic changes due to the use of indomethacin.

Cerebral and gastrointestinal side effects, generally mild and usually transient, occurred most often after prolonged administration of the drug. Of the eight patients who experienced 13 side effects, 4 were taking 200 mg. of indomethacin daily. Side effects persisted in 2 of these 4 patients until their maintenance dosage was reduced. Otherwise all side effects disappeared spontaneously while the drug continued to be taken.

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**Dr. LAWRAZON.** Mr. Chairman, the second presentation to the committee will be from a man with long experience in the problems of management of rheumatoid arthritis and other arthritic disorders, a man who has addressed himself to drug evaluation and a leader in the professional society, the American Rheumatism Association. I would like to present Dr. Charley Smyth, a professor of medicine and head of the Division of Rheumatic Diseases at the University of Colorado School of Medicine.

Incidentally, he is also past president of the American Rheumatism Association.

**Senator NELSON.** Doctor, we appreciate your coming here today and your patience in waiting so long to testify. Your curriculum vitae will be printed at this point. Please proceed.

(The curriculum vitae of Dr. Smyth follows:)

## CURRICULUM VITAE, CHARLEY J. SMYTH, M.D.

Born: Mart, Texas, February 7, 1909.

Education: University of Michigan, AB Degree, 1931; University of Michigan, MS Degree (Pathology), 1938; Jefferson Medical College of Philadelphia, M.D. Degree, 1935.

Internship: University of Michigan Hospital, 1935-1936.

Residency: University of Michigan Hospital, Medicine, 1936-1938; Pathology, 1938-1939; Fellowship, Arthritis, 1939-1940.

Professional appointments: Assistant Physician—Rackham Arthritis Research Unit, University of Michigan, 1939-1941; Medical Director—Wayne County General Hospital, Eloise, Michigan, 1941-1949; Assistant Director, Graduate and Postgraduate Medical Education, Univ. of Colo., 1949-1950; Director, Graduate and Postgraduate Medical Education, University of Colorado, 1950-1954; Editor, Rheumatism Reviews for American Rheumatism Assn., Part time 1956-1958.

Present position: Professor, Internal Medicine, University of Colorado, in charge of Rheumatic Disease Section, 1967-present.

Academic appointments: Instructor, Internal Medicine, 1939-1942, University of Michigan, Ann Arbor, Michigan; Instructor, Internal Medicine, 1949-1950, Wayne University, Detroit, Michigan; Assistant Professor, Internal Medicine, 1949-1950, University of Colorado; Associate Professor, Internal Medicine, 1950-1967, University of Colorado; Professor, Internal Medicine, 1967-present, University of Colorado.

Certification of specialty board: American Board of Internal Medicine, 1950.

Hospital appointments: Consultant, Internal Medicine, Fitzsimons General Hospital, 1950-present; Consultant, Internal Medicine, Denver Veterans Administration Hospital, 1950-present; Consultant, Internal Medicine, St. Joseph's Hospital, Denver, 1953-present; Consultant, Internal Medicine, St. Luke's Hospital, Denver, 1953-present; Consultant, Internal Medicine, General Rose Memorial Hospital, Denver, 1953-present; Consultant, Internal Medicine, Mercy Hospital, Denver, 1953-present; Consultant, Internal Medicine, Presbyterian Medical Center, Denver, 1953-present.

International, national, State and county organizations: Committee appointments, Board of Directors and Executive Committee, Arthritis Foundation (National), Vice President La Lingue Internationale Contre Le Rheumatisme, 1965-present.

Professional society memberships: Governor for Colorado, American College of Physicians, 1960-present; American Society Internal Medicine, Committee on Academic Membership, 1965-present; Board of Directors and Executive Committee, Rocky Mountain Chapter, Arthritis Foundation, 1950-present; Central Society for Clinical Research, 1939-present; American Federation for Clinical Research, 1942-present; American Rheumatism Association, 1940-present (President 1960); American College of Physicians, Fellow, 1951-present; Society Experimental Biology and Medicine, 1942-present; American Therapeutic Society, 1958-present; Colorado Society of Internal Medicine, 1952-present (President 1957-1958); American Society of Internal Medicine, 1957-1968 (Trustee 1967-present); Denver County and Colorado State Medical Society and the American Medical Association, active member, 1949-present; American Society of Clinical Rheumatology, 1960-present (President 1964).

Honorary scientific societies: Sigma Xi, Michigan, 1939; Alpha Omega Alpha, Jefferson Medical College, 1935.

#### STATEMENT OF DR. CHARLEY J. SMYTH, PROFESSOR OF MEDICINE; AND DIRECTOR, DIVISION OF RHEUMATIC DISEASE, UNIVERSITY OF COLORADO MEDICAL CENTER, DENVER, COLO.

**Dr. SMYTH.** Senator Nelson, it is an honor. I am deeply grateful for this opportunity to present my views concerning the results of treating arthritic patients with indomethacin.

My major responsibilities include the care of patients seeking relief of pain and disability in two large weekly arthritis clinics at the Colorado General Hospital. In addition, I see and examine, as a consultant, patients in the Denver Veterans Hospital, the Fitzsimons Army Hospital, and other unfortunate victims with various types of arthritis in other hospitals in Denver. I estimate in an average week, I pass judgment and recommend treatment upon 75 to 80 individuals affected with one form or another of arthritis.

In the 30 years that I have worked with arthritic patients I have dealt firsthand with many new compounds. The most exciting and promising was cortisone, introduced in 1949. I witnessed the phenomenal rise and slow decline in its popularity as the sad ill effects of its long-term use made their appearance in the clinics, on the hospital wards, and, unfortunately, at the autopsy table.

Therefore, it was with great interest that I and many other of my colleagues in clinical investigations treating rheumatic diseases began studies with the promising new compound indomethacin in 1963.

It had clearly been demonstrated in experimental animals. It looked as though it were more powerful than cortisone or any of the other then commonly used drugs in the treatment of arthritic patients.

It soon became apparent that this drug quickly controlled the pain and inflammation of gouty joints. After treating 30 patients with acute gout and observing uniformly favorable results with minimal side effects we reported our experiences in Stockholm, Sweden, before the European Congress on Rheumatic Diseases in 1965. Other critical clinicians throughout the world have since confirmed these early studies, and today there is general agreement that this drug is as effective and as safe as any other in the treatment of acute attacks of gouty arthritis.

Our next effort in the area was to investigate patients with rheumatoid arthritis of the spine. Dr. Calabro has told you of his investigation of this variety of arthritis affecting healthy young men in which the disease attacks mostly the spine. The results were excellent, and the drug was well tolerated. Many of these patients were confined to bed, but returned to gainful employment within weeks after the beginning of therapy with this new compound. Other investigators have made similar observations, and today there is no debate about the value of indomethacin in patients with rheumatoid arthritis of the spine.

There is still some controversy about the use of indomethacin in rheumatoid arthritis. This is the great crippler and one of the commonest of the rheumatic diseases. It is in this type of arthritis that the clinical investigator has the greatest difficulty in evaluating drugs, or indeed the effect of any procedure.

I refer primarily, Senator, to the procedure called synovectomy that the orthopedic surgeons are now doing; that is, taking out joint membranes for this disease. We have had great trouble in deciding whether these procedures are really justified or not. They are being done throughout the world without any proof that they are actually beneficial to the patient.

So the course of this disease, as you already have heard, fluctuates up and down, notoriously rises spontaneously and suppresses spontaneously, whether you treat the patients or do not treat them. Furthermore, it has been expressed repeatedly before your committee that there is no satisfaction or sense of security in the methods of testing either a surgical procedure (synovectomy) or a new drug that is handed to the clinician with the question: Is this or is this not an effective agent in this capricious, fluctuating illness?

Our group undertook this difficult problem of attempting to evaluate indomethacin in 1963. We devised a series of objective tests—not including the patient's symptom response—with the aim of expressing a reliable opinion. These studies were based upon the best objective measurements available and conducted by an experienced clinician. To control our data further, we included periods of therapy using placebo capsules, during which neither the patient nor the doctor knew whether his patient was actually taking the real drug or a "dud" pill. In 1965 we published our experiences with 55 patients with rheumatoid arthritis treated with indomethacin. In that report we stated, "Indomethacin suppresses joint inflammation and improves joint function, but may require up to 2 to 4 months to obtain maximum therapeutic

effort." With 3 additional years of experience in treating more than 100 rheumatoid patients under the same rigidly controlled conditions of objective evaluation, I am still of this same opinion.

As I have previously stated, but a point that must be emphasized, the course of rheumatoid arthritis varies continuously with spontaneous flareups and remissions. Therefore, it is extremely difficult to obtain completely reliable data concerning the benefit of any drug or procedure. We are continuously altering our objective tests, and we have recently devised a skin temperature device in which we will put a thermister, which registers joint temperature, directly on the skin over the joint to critically measure skin temperature to see if this can be a more objective measure of gaining reliable information in this area of clinical drug testing.

Now, if I were to express an opinion about the frequency with which responses occur in rheumatoid arthritis, recognizing fully these limitations which all of us agree to, I would say that 20 to 25 percent of rheumatoid patients treated with adequate doses of this drug do show objective improvement; an additional 20 to 30 percent report symptomatic relief.

I think it should be stressed that when a reliable investigator administers this drug to his patients, the results in indomethacin response are definite; you do not need the statistician to tell the experienced clinician that his patient is better. For this reason I am convinced, as are many other reliable observers who care for rheumatoid patients, that indomethacin is effective in some cases when other agents have failed.

It is claimed by some observers who have appeared before this committee that peptic ulcers are common in rheumatoid patients treated with this drug. I would stress that this is true of any effective anti-inflammatory agent. In other words, if aspirin or any other commonly used antirheumatic drug is taken, it is potentially ulcerogenic or potentially an ulcer-forming agent. My colleagues at the University of Colorado and I have analyzed on our own initiative, because of our interest in the scientific question: Is indomethacin ulcerogenic? We have analyzed now 299 patients treated with indomethacin at the University of Colorado Medical Center during the past 5 years. As a control, we took 65 rheumatoid patients in the same clinics who had received aspirin or other commonly used antirheumatic drugs. This statement I would like to emphasize and bear down upon, because I think that it is the first comparative study that has ever been reported. There was no difference in the frequency of peptic ulcers in these two groups of patients. These studies do not support the view that indomethacin is ulcerogenic.

In the final analysis, it is the arthritic patient himself who decides if any drug is worth taking. If he does not get relief from his joint aches, pains, and stiffness, from a prescription, his physician hears about it on the next visit. It is not the advertising campaign of the drug manufacturers that convinces the practitioner of the virtues and safety of a new drug. His judgment of the benefits and reliability of a drug is based upon his own personal experience gained from listening to and examining his patient.

SENATOR NELSON. Are you referring to all drugs?

DR. SMYTH. I did not say so, sir. I could broaden that if you wish me to say so.

**Senator NELSON.** Oh, no. You said that, "It is not the advertising campaign of the drug manufacturers that convinces the practitioner of the virtues and safety of a new drug. His judgment of the benefits and reliability of a drug is based upon his own personal experience gained from listening to and examining his patient."

**Dr. SMYTH.** I think I will qualify that to arthritic drugs, sir.

**Senator NELSON.** Thank you.

**Dr. SMYTH.** As I look at indomethacin from the vantage point of 5 years of practical experience, coupled with my knowledge of the many reports from other parts of the world, this drug has established a place in the treatment of arthritic patients. Furthermore, it has achieved a reasonable degree of both patient and physician acceptance in large-scale clinical use, which, in the final analysis is the only true test of any therapeutic agent or procedure. I would be handicapped in the management of many arthritic patients without this drug.

(The attachment to Dr. Smyth's statement follows:)

#### MEDICINE—AN ART AS WELL AS A SCIENCE

In spite of the truly miraculous advances in the sciences of chemistry and pharmacology that synthesize and bring from the laboratory to the doctor new drugs for trial, there are still some factors that are unique in determining the true value of a new drug in a human being. The practice of medicine is not a pure science; it is both an art and a science. In men and women with arthritis of rheumatoid type there is no simple magic test that gives us yes and no answers. Unfortunately, as of now, this is not so. Judgment or medical opinion in weighing the effectiveness or the lack of it with a drug like Indomethacin is based upon experience and previous responses using other, better understood anti-rheumatic agents.

**Dr. SMYTH.** I am extremely grateful to you, Senator Nelson, for permitting me the opportunity to appear before your committee. Thank you very much.

**Senator NELSON.** Doctor, the committee appreciates your taking the time to come here and testify.

As to your last sentence, I hope you do not have the impression that we have had witnesses from the FDA and elsewhere who said that indomethacin should not be in the marketplace.

**Dr. SMYTH.** This is my impression, from the testimony of FDA and others included, that this drug should not be used, medical evidence notwithstanding.

**Senator NELSON.** You mean it is your opinion that testimony has been presented that this drug should not be available to the public?

**Dr. SMYTH.** Yes.

**Senator NELSON.** No; I thought in the last sentence, there was an indication that you believed that witnesses before this committee recommended that the drug be taken off the market.

**Dr. SMYTH.** Senator, these remarks have been prepared in Denver. They appear exactly as printed.

**Senator NELSON.** I thought you had the impression that some of the witnesses were saying this drug did not have any value. But, the general consensus, as I understood it from the witnesses who have testified today and on previous days, is that this drug has an appropriate place in the physician's armamentarium.

**Mr. GORDON.** Doctor, I just want to ask one question.

I read an article by you in a magazine called *Consultant*, issue of April 1967. It is entitled, "Treating Rheumatoid Arthritis, What Is Most Apt To Succeed?"

You discuss steroids and the value of short-term treatment. You discuss phenylbutazone as a drug for the management of rheumatoid arthritis, the antimalarials, gold, orthopedic surgery. But except for mentioning indomethacin in passing, you do not discuss that at all. Why?

**Dr. SMYTH.** There is a limit to which you can go in an article of that type. It is very restricted, was highly edited by the editor of this journal, *Consultant*. I just did not have enough time to amplify my opinions about indomethacin in that brief report. I think my presentation today before this committee explains my position much more fully than I was able to do at the time this article was written.

**Mr. GORDON.** Thank you.

**Senator NELSON.** Thank you, Doctor.

**Mr. GADSDEN.** Is it your wish that I should continue? I will be the final witness for Merck.

**Senator NELSON.** Please proceed.

**STATEMENT OF HENRY W. GADSDEN, PRESIDENT, MERCK & CO., INC., RAHWAY, N.J.; ACCOMPANIED BY LLOYD N. CUTLER, SPECIAL COUNSEL, WASHINGTON, D.C.**

**Mr. GADSDEN.** Thank you, sir. I would like again to express my appreciation for my associates and myself for the early opportunity to get this on the record.

I would like first to explain why I plan to focus my remarks before the committee on advertising and promotion. I am a layman, and it seems appropriate that the medical and scientific issues of interest to you should be discussed by the most highly qualified professionals. I do not feel that I could add anything to the profile of "Indocin" that has been drawn today by Dr. Beyer and Dr. Lawrason.

On the other hand, the philosophy that animates our advertising and promotion is not only a subject of continuing concern to me, but also one for which I can properly accept a very direct responsibility.

As president of Merck, I wear many hats—one as chairman of our new products committee. That committee, as one of its major responsibilities, seeks to make sure that the marketing profile of a drug corresponds in every respect to its medical profile.

It is Merck's policy to avoid the possibility of including any questionable statement or theme in any of our advertising or promotion. The mere fact that any point is validly challenged, in or out of the company, leads us immediately to change or remove the point under discussion. I have repeatedly made this policy clear to my associates, as the following excerpts from my memorandum of May 1966 to top executives of the company will make clear:

We seek to convey through both the parts and the whole of each advertisement a factual message which will be useful and interesting. Never must the ad seek to obscure a blemish for the sake of over all appeal. \* \* \* We seek to provide sharper focus and greater perspective so that the reader, viewer, or listener will make his own decision. These principles are so cardinal to the success of our operations as to warrant periodic re-emphasis. \* \* \* Please take this occasion to re indoctrinate all of your people who have a responsibility for our advertising, and follow this up with reminders at appropriate intervals.

More specifically, our internal procedures require that every piece of advertising and promotion must have the approval of a physician and a lawyer, who are responsible for its medical accuracy and conformity with law. When it concerns a new product, it also undergoes final review by the new products committee.

The safeguards are necessary and proper. But I would not have you think that I conceive of advertising and promotion primarily in negative or restrictive terms. Properly carried out, it serves an altogether good and socially valuable purpose.

Through the process of discovery we have described for you, making a drug available is only the first long step toward the objective of having it used by those patients who need it. This objective can be attained only if physicians are aware of the availability of the drug, know what it can do, what its limitations are, and what undesirable effects may accompany it. Furthermore, we believe that this information should reach the physician as quickly as possible. The public interest would be poorly served if patients were denied the benefits of a good drug simply because its availability was not known.

Merck's experience with Benemid, a product for the treatment of gout, illustrates how marketing decisions can have social value. When we introduced Benemid in 1951, we felt that it was a major product because it forestalled attacks of gout instead of merely giving relief after an attack. Sales did not approach anticipated levels for years, apparently because there were simply not sufficient cases of gout. We continued to inform physicians about it, however, in the belief that gout was more prevalent than sales indicated. The past 8 years have justified this belief. The estimated number of cases of gout under treatment has risen from fewer than 350,000 in 1959 to approximately 1 million in 1966. Obviously, the incidence of gout has not increased threefold since 1959.

**Mr. GORDON.** Is this due to your advertising?

**Mr. GADSDEN.** As I am going to say, Mr. Gordon, in the next sentence, we would like to take partial credit for increasing the awareness of the symptoms of gout.

Recognition and subsequent treatment of gout have increased—due in part, we believe, to our communications program.

I have described the precautions we take with our advertising. Nevertheless, an occasional advertisement does run into trouble with the FDA. I think the reasons can be found primarily in the changing regulatory climate, and in the turnover of officials responsible for interpreting and applying the advertising regulations. As official attitudes have become increasingly critical of the motives and methods behind the advertising of prescription drugs, more and more companies have been embroiled in disputes with the FDA.

However, questions of interpretation to one side, Merck hopes and believes that the agency shares our belief that responsible and effective promotion is a necessity. It is particularly necessary in the case of a drug which offers the possibility of benefits to patients suffering from conditions for which there is as yet no fully effective or satisfactory method of treatment. Arthritic disorders represent just such a condition. Some patients obtain little or no relief from drugs which are available; side effects limit the benefits others may obtain. The availability of a new drug which can help those who cannot obtain relief from other measures becomes important.

As Dr. Donald F. Hill stated in his presidential address to the American Rheumatism Association in June 1967:

Our patients come to us discouraged. Arthritis is a discouraging disease. Too many of our patients are further discouraged by what the doctor tells them. Too many of them hear him say: "There is not much we can do for you."<sup>1</sup>

Our failure to keep up with, and apply, the latest treatments and medical information in arthritis may not have . . . final and fatal results, but if it means the difference between a useful and productive life, or a life as a cripple, the point may be lost on the patient.<sup>1</sup>

It is true that a company promotes a drug in order to sell it. But such a statement is an oversimplification which ignores the full facts. A drug sells because it is promoted, and because physicians are familiar with it, and finally because they have found that it fills a real need in their practice.

That Indocin does fill such a need in medical practice has been amply demonstrated. The purpose of clinical investigation is to assure safe and effective medicines. Added evidence that we have provided such a medicine in Indocin is to be found in the high refill rate of prescriptions for this drug. Because it is a useful drug, it deserves appropriate promotion.

We have promoted Indocin in many ways, but have consistently sought to follow the principle of supplying accurate and useful information in a manner complying with our understanding of the regulations.

When Indocin was first made available in this country, we had accumulated experience based on nearly 5 years of investigation by more than 300 physicians in the United States and abroad, as well as extensive experience gained from overseas marketing. Our best knowledge was incorporated into our promotional materials.

The initial promotion pieces very clearly stated that in patients with rheumatoid arthritis, ankylosing spondylitis, arthritis of the hip, and gout—the four indications for which the safety and effectiveness of Indocin had been established—overall improvement considered to be excellent or good had been reported in 65 percent of those patients. This not only established the usefulness of the drug to the physician but, equally, it advised him that the drug had limitations and could not be considered effective in all patients.

Furthermore, prominently presented in these promotional pieces was a table showing the incidence of adverse reactions. It not only listed those adverse reactions the physician could expect to encounter, but what their probable incidence would be. And it also included the statement:

In about 10 to 15 percent (of the patients), adverse reactions may be of a severity requiring dosage reduction or discontinuance of therapy.

After the introductory phase of our promotional efforts, and as physicians became more familiar with the drug, our themes were varied, but our presentations continued to include the limitations of the product. In many of the advertisements the negative aspects of the drug actually consume the bulk of the text.

As my scientific colleagues have stated, many, if not most, distinguished rheumatologists believe that the use of objective measurements alone in arthritic disorders fails to take adequately into account the

<sup>1</sup> "Progress for the Patient," Hill, Donald F., M.D., "Arthritis and Rheumatism," vol. 10, No. 5 (October 1967).

disease process involved. And even more importantly, the use of these measurements alone ignores the subjective benefits enjoyed by the patient. No claim has ever been made that Indocin has any effect on the basic disease processes involved in arthritic disorders. The only claim made has been that in some 65 percent of the arthritic patients who are placed on Indocin, their stiffness, swelling, tenderness, and pain—which are manifestations of their disease—are relieved. These are the reasons that these patients seek medical help, and the relief of these symptoms is an important benefit to the patients and a source of satisfaction to the physicians who have prescribed the drug.

There is nothing new about the purely statistical approach—as opposed to the clinical approach—to the measurement of the effectiveness of a drug such as Indocin in conditions such as arthritic disorders. Few physicians would dispute that the corticosteroids can provide dramatic relief to many arthritic patients in whom all other measures have failed. Yet in 1960, the following statement appeared in the journal, *Annals of Internal Medicine*:<sup>1</sup>

Reports of the Medical Research Council and Nuffield Foundation and the Empire Rheumatism Council indicated no significant difference in results of treatment between two groups of patients, one on cortisone and the other on aspirin. However valid these results statistically, purely functional therapeutic effects of steroids in certain individual patients were still impressive. Since none of these drugs affected the disease fundamentally, the question was whether cortisone had not in some instances enabled the patient to "get more out of life," though happiness is not a scientific quality.

The education of the physician is long and intensive. I think it is fair to say that to succeed in the practice of medicine, much more than in most professions, one must be able to make valid judgments of cause and effect. On the basis of his training and experience, the physician tries a drug in a patient. On the basis of his observation of the effect the medicine produces, he decides whether to continue it. His attitude toward the drug, and certainly toward the promotion relating to it, is continuously watchful and thoughtful—just as it is toward his patient. For example, the physician must evaluate the history of the patient's complaints, determine the significance of his findings on physical examination, and assess the results of laboratory tests before he can arrive at a diagnosis. Equally, he must be critical of the results he obtains from any therapeutic regimen. And if for any reason he is not, you can be sure that his patient will be.

I wonder if any of you gentlemen on the committee or its staff ever have suffered from a recurring pain? Speaking as one who has, I venture the opinion that you could not be deceived—certainly not for long—about whether a drug gave you relief. Well, the patient with arthritis comes to his physician for relief. If he does not receive it, he will want an explanation, or else he will seek relief elsewhere—regardless of the drug advertising his doctor may be exposed to.

To suggest that a physician is uncritical is completely to ignore the realities of the situation. Promotion may assure a physician's interest in a drug, but promotion cannot substitute for results.

There is no doubt in my mind that when physicians feel there is a need for a new drug in their practice, promotion can induce them to try one that offers promise. It is equally certain, however, that promo-

<sup>1</sup> "Thirteenth Rheumatism Review": *Annals of Internal Medicine*, vol. 53, No. 7, Dec. 30, 1960, p. 49.

tion cannot persuade them to continue prescribing the drug unless they themselves find that it fills a real need in their practice. Indeed, the history of medicine is replete with examples of drugs whose early promise was not fulfilled, and whose sales were equally unsatisfactory.

**Senator NELSON.** I would like to make the point, however, that chloramphenicol is one item which was heavily promoted, and the promotion was very effective; there is no question about that. The promotional activities were effective and there were disastrous results because the drug was prescribed and used for nonindicated cases. That is part of the issue on which we have been conducting hearings here.

Certainly the doctors got dramatic results. One of the distinguished physicians testified—I think it was Dr. Dameshek—that he had a patient who had been taking chloramphenicol prescribed for a cold. His patient told him that the doctor told her to take it home, put it on the bathroom shelf, and take it every time she had a cold. It sure wiped out the cold for all time, but it killed her, too.

This is one dramatic case where the promotion of the drug resulted in a vast overprescription of the drug, which caused Dr. Goddard to say before this committee, "I am at my wits end" as to how to persuade doctors not to use this drug for nonindicated cases.

That is what the hearings are about, the effectiveness of the promotion of drugs. Here is a case where the promotion has been fantastically effective, with disastrous results for many, many patients. I have scores of letters in my office from people about relatives who have died from taking this drug. One doctor prescribed it because he had been told by a detail man that there were no side effects. He prescribed it for his son for a minor infection. The child developed aplastic anemia and died.

Well, the evidence is that promotion is effective and very often doctors do not pay any attention to the precautions that are written in the labeling and that very effectively, in their advertising, drug companies manage with the cleverest advertising agents in America, to kind of skip over the side effects.

We had testimony on the advertising of your drug on this exact point. Yesterday we heard testimony that in JAMA, the language used was that Indocin was "(a) drug of choice."

**Mr. GADSDEN.** Yes, sir.

**Senator NELSON.** Well, everybody knows that the phrase "drug of choice" are words of art in the medical field and that they have a very special meaning and that to put the word "a" in brackets does not prevent doctors from thinking that it is "the" drug of choice. I think it is misleading.

But in any event, I have seen example after example of the very clever wording which is aimed at playing down side effects, playing down contraindications, and expanding claims for a drug's use.

I am not criticizing your company especially. I think every single company I have looked at that uses ads does not tell the story as accurately in the ad as they tell it in the package insert which has to be approved by FDA.

**Mr. GADSDEN.** Senator, if I may respond—you can understand, I imagine, my continued sensitivity to perhaps the inadvertent reference to chloramphenicol within the context of our discussions about in-

domethacin. So I would like to read something to that point into the record.

Senator NELSON. The reason I referred to it is that your language was in the most general kind of terms as were used for chloramphenicol or many other drugs. Chloramphenicol happens to be one of the dramatic examples heard before the committee, standing unrefuted by the company or anybody else that I know of, of the wide misrepresentation of a drug because of the type and intensity of promotional activities.

Mr. GADSDEN. But I think there is a differentiation between the point that I was making, which related to effectiveness—the patient and the physician cannot be fooled over an appreciable period of time by an effective drug—and the issue which you raised about whether the physicians did or did not pay attention to whatever might have been known about the safety of chloramphenicol.

Senator NELSON. Well, I would suggest that they were not fooled in this case over any period of time about an ineffective drug. It was a dramatically effective drug, but was being used for the wrong purpose. It no doubt had an effect on infections, but it also may cause fatal aplastic anemia. It was just being incorrectly used.

Mr. GADSDEN. With your permission, may I make a statement on this point?

Senator NELSON. Yes.

Mr. GADSDEN. Chloramphenicol is an extremely potent antibiotic drug with a propensity to cause aplastic anemia which often results in a fatality. Indomethacin has no adverse effect even remotely approaching this condition. Chloramphenicol, although uniquely valuable for some infectious diseases such as typhoid fever and staphylococcus infection, can often be replaced in the case of other infectious diseases by different antibiotics with less severe side effects. Indomethacin, on the other hand, does not have greater adverse effects than most of the other drugs available for treating certain classes of arthritic disease. Moreover, patients suffering from arthritic diseases do not uniformly respond to the same drug. While it may be that aspirin has fewer adverse effects than indomethacin in the massive doses needed to treat rheumatic disorder, although this has not been proved, there are many arthritic patients who cannot tolerate aspirin or who do not respond to it.

Dr. Hodges estimated the number who cannot tolerate aspirin at 25 percent. Many such patients do respond to indomethacin and do not suffer greater adverse effects than those caused by other, alternative treatments.

Dr. Hodges has summarized for you the many severe side effects that result from the corticosteroids, the butazones, the antimalarials, and gold salts, and you can see that indomethacin compares favorably with any of these alternatives.

Accordingly, any suggested parallel between indomethacin and chloramphenicol is, in my opinion, extremely farfetched.

Senator NELSON. Has anybody suggested a comparison?

Mr. GADSDEN. Sir, I am paraphrasing.

Senator NELSON. I have not suggested a comparison?

Mr. GADSDEN. I apologize for my undue sensitivity.

Senator NELSON. I want to make it clear for the record that I was responding to a statement in your testimony that had nothing to do with indomethacin in particular, or any drug in particular. The sentence was: "It is equally certain, however, that promotion cannot persuade them"—that is, the doctor—"to continue prescribing the drug unless they themselves find that it fills a real need in their practice."

Part of these hearings is directed to the question of the promotion. The point I was making is that you, again, persuade them by promotion to use a drug in their practice that is effective for the purpose for which they use it but should, for the sake of safety, be used with much greater discretion. That is my comment. I was not comparing it with indomethacin at all.

Mr. GADSDEN. There is one other point that you made, Senator. Referring to the quote which did, in fact, appear in our ads—this was a factual quote from a recognized authority.

Senator NELSON. Which quote?

Mr. GADSDEN. The one about "a drug of choice." In fact, the actual quote says, "the drug of choice." Under AMA editorial policy, they do not permit you to say "the" drug of choice; so if you check our advertisements, you will find that we ran both advertisements. In the JAMA, we said "a drug of choice"; in the others, we used the language of the quote itself, which is, "the drug of choice."

I would furthermore like to call your attention to a quotation of 1967 from the recognized publication, New Drugs, as published by the AMA. It says that because "Indocin" has produced relief in acute attacks within 48 hours, and because it lacks the untoward effects of Colchicine, some physicians consider it to be the drug of choice for these attacks.

Shall I proceed, sir?

Senator NELSON. Yes, go ahead.

Mr. GADSDEN. Mr. Chairman, Indocin has demonstrated its ability to fill this need in the practice of physicians, both in this country and around the world. If it did not fill a need, the past 3 years of experience with it would have clearly demonstrated this fact.

I do not challenge the sincerity of some who have said that in our promotional efforts we made some errors. Language is not a perfect method of communication, and it may well be the words and phrases that we used in the belief they meant one thing may have been interpreted by some physicians to mean something else. Such are the complexities of semantics. But this was never done purposely, and whenever any possibility of misunderstanding was called to our attention, we moved promptly to correct it. If we have made errors, they were only minor ones, and to the degree that they existed they were hemmed in by the total emphasis given to the relative effectiveness, safety, and limitations of the drug.

We responded immediately to negative comment by the FDA, and the advertisement which they complained of has not appeared since November 1966. We took this action primarily from a prudent desire to cooperate with the Agency. We hope that upon the completion of the computer tabulations of our entire patient data, we can discuss with the Agency the renewed use of such claims as "Extends the margin of safety."

Senator NELSON. What does the phrase, "Extends the margin of safety," mean?

Mr. GADSDEN. In the context in which this was discussed, in the advertisement and as positioned by our scientists and medical personnel based upon their own knowledge and primarily that of clinical investigators, when compared to the drugs which have been mentioned here before, butazones and corticosteroids, it says that more patients can be treated with Indocin with fewer side effects.

Senator NELSON. That is what "extends the margin of safety" means in this case?

Mr. GADSDEN. Yes, sir.

Senator NELSON. Please continue.

Mr. GADSDEN. Indocin has established its place in medical practice because it has demonstrated effectiveness in many patients with certain arthritic disorders, at the same time being relatively safe for most patients to take over the long periods of time they must remain under treatment.

In closing, I would like to make one general point. Merck has been making and marketing a lot of drugs for a long time. It has been a point of pride with us—and an essential element in our success—to provide good, reliable information on these drugs and their proper use. The record will show that our batting average has been very high. And the people who have benefited from them are, I submit, the best evidence of the social values of our products and the way we market them.

Mr. Chairman, thank you again for the opportunity of appearing before you. If you have any further questions, my associates and I are at your disposal.

Senator NELSON. Thank you, Mr. Gadsden, for your very thoughtful contribution to these hearings. I believe the minority counsel has a question.

Mr. GROSSMAN. Yes, Mr. Gadsden. I would like to ask you about the article that appeared in Pageant. I think that the company issued a release yesterday, but I would like to get it clear for the record, because that matter did not go into the record. I would like to know first of all, and I think you can make a general statement if you wish, but first, is it true that Merck & Co. in no way initiated that article or paid for it in any way and that these people were completely acting on their own. Is that correct?

Mr. GADSDEN. We neither initiated nor paid for nor stimulated it, nor did anything except what I referred to in my earlier testimony.

Mr. GROSSMAN. So in other words, for the record, so that we have it clear, there was no dealing with Pageant magazine or with the authors of the article?

Mr. GADSDEN. No, there was not.

Mr. GROSSMAN. May I ask you, is soliciting material from you common procedure among individuals who write these articles? Do you think there is any way of controlling this? Is it an abuse that industry can handle?

Mr. GADSDEN. I think we are into an area here which is very difficult, if I may be presumptuous, for you or for us on what to say or what not to say. In other words, we have a free press in the United States. You have recognized scientific writers who quite naturally wish to inform the public upon what they consider interesting developments. We have to toe a very close line as between deciding that we will withhold

information from the press completely and thereby run the risk that what is printed is completely misleading, as contrasted to using our best judgment as to what we should supply in the interest of a balanced presentation.

Mr. GROSSMAN. What are your general feelings about articles that reach beyond the doctor, such as this one; in other words articles directed at the general public?

Mr. GADSDEN. This is the type of article to which I am referring. So that we may be completely clear, when I say "science writers," I am referring to science writers for lay publications as contrasted to professional journals.

Mr. GROSSMAN. I agree with your point about the freedom of the press. I am just getting a general impression of what you think about this.

Mr. GADSDEN. Well, I guess I am fairly pragmatic on this subject. Regardless of whether we think it is appropriate or inappropriate, the fact remains that the public has become increasingly interested in anything to do with health. There have been any number of articles. I think that within the restraint under which we must place ourselves—one is that we must obviously comply with the food and drug regulations and other laws of the land—within our interpretation of that, we should attempt to see that what appears in print is as factual as possible.

Mr. GROSSMAN. One other question in a different area. There has been some testimony and some inference that there is no truly independent research being done, in the sense that there is an inherent conflict of interest, almost, in that you have firms to do your clinical research and report their objective findings. I wonder what comments you might have on idea that, for example, the Government might select that specific consultant for the company, the company would pay for it, and submit the findings to the FDA for approval?

Mr. GADSDEN. First, as temperately as possible, I would like to resent the implication that a company such as Merek either could or would attempt to doctor the results.

Mr. GROSSMAN. That is not my question.

Mr. GADSDEN. I realize that. I just want to get that on the record, if you will permit me, because we have been in business for a long time and we could not risk our reputation this way, even if we could "buy results."

Now, some of the previous witnesses before this committee have raised a question as to the integrity of the drug companies or the clinical investigators, who in the main are connected with academic institutions. Well, on their behalf and gratuitously, I resent it for them, too.

Also, one of your witnesses before this committee raised some rather serious doubts in his testimony about whether civil servants would assume the responsibility of making a decision if there were a gain-risk balance, and someone had to assume the responsibility.

Mr. GROSSMAN. I think this is the FDA's decision.

Mr. GADSDEN. I think what I am suggesting is that we are pretty soon in a never-never land. There may be a fourth party, but I cannot identify it at the moment. Questions have been raised as to whether the pharmaceutical companies can do it, or whether it can be ap-

propriately done under grant by academic people; now we have finally completed the circle by saying that, in the opinion of at least one witness, there is question as to whether someone who is a Government employee will assume this degree of responsibility. I am frankly lost with this kind of, if I may, sophistry.

In our opinion, the procedures which have been described by my scientific colleagues have, in fact, yielded very good results. This is what I referred to in my statement. We are in the happy position—in regard to these products which Dr. Tishler has described, starting with the vitamins and bringing it up to date—that there have been very rare occasions when the initial positioning of a Merck product had to be seriously modified based upon experience in the marketplace.

Mr. GROSSMAN. Thank you.

Senator NELSON. Thank you very much, Mr. Gadsden. If you have any additional pertinent material which you have neglected to give us for the record today, the record will be open for another week. If at any time in the course of these hearings, you wish to make any contribution concerning any issues raised before the committee we shall be pleased to have your material.

Mr. GADSDEN. Thank you for that opportunity, Senator. Even before these hearings, in the telephone conversations which I had with Mr. Gordon—I think that Mr. Cutler has had subsequent ones—we asked for the opportunity, if it seemed appropriate, to file supplementary statements based upon testimony that was given between the time we prepared our statements and our presentation here, because we had to do this on very short notice and we compressed it within a limited period of time.

(Subsequent correspondence and supplemental statements were submitted by Merck & Co., Inc., and follow:)

MERCK & CO., INC.,  
Rahway, N.J., May 14, 1968.

Hon. GAYLORD NELSON,  
Chairman, Subcommittee on Monopoly, Select Committee on Small Business,  
U.S. Senate, Washington, D.C.

Dear SENATOR NELSON: I am enclosing several supplementary statements for inclusion in the record of the hearings of your Subcommittee relating to 'Indocin'. We appreciate your willingness to permit us to file these supplementary statements and your recognition that we could not deal in our prepared statements with the testimony of witnesses who immediately preceded us.

We believe that the testimony we presented on May 3 and the statements of Dr. Hodges, Dr. Rothermich, Dr. Calabro, and Dr. Smyth constitute a sufficient response to most of the testimony of the academic witnesses who testified on April 23 and 24.

We have prepared, however, and submit herewith supplementary material bearing on two aspects of Dr. O'Brien's testimony: an internal memorandum by Dr. Hurwitz of the FDA, apparently overlooked by Dr. O'Brien, which revises the views Dr. Hurwitz expressed in an earlier memorandum that was critical of the clinical studies with 'Indocin' and that was quoted from at length by Dr. O'Brien; and a statement of Merck's policies and procedures in the support of clinical investigation.

In connection with the May 1-2 hearings, we are also submitting supplementary material related to the testimony of Dr. Jennings and Dr. McCleery of the Food and Drug Administration, who dealt primarily with the content of our labeling and advertising and with our performance in promoting 'Indocin'.

Implicit in Dr. Jennings' and Dr. McCleery's testimony were suggestions that the Company and its executives acted on the basis of motivation to overstate claims, minimize adverse effects, expand use of the drug beyond allowed claims, and resist efforts of the Food and Drug Administration to enforce proper standards of communication to doctors.

It is difficult to present objective evidence in rebuttal of these subjective imputations. We would remind the Subcommittee, however, that there is a common sense and essential logic in our position that any such motivation would inevitably damage our reputation with the doctor and the patient, and would be detrimental to our business interests in the long run. Since our business is uniquely dependent on what the health professions think of or character and reputation, it would make little sense for us to engage in this kind of conduct—and we do not do so.

As I said in my direct testimony, it is not the Food and Drug Administration that is ultimately responsible for the safety and effectiveness of our products, including the information we give to the doctor about them. It is we who must bear that responsibility and who must suffer the consequences of failure. This is the way it should be, and this is the way the Food and Drug Administration should want it to be.

We would appreciate your placing these materials in the record at the end of the testimony of Dr. O'Brien, Dr. Jennings, and Dr. McCleery respectively, and request that this letter be placed at the end of the Merck testimony on May 3.

Sincerely,

II. W. GADSDEN, President.

**SUPPLEMENTARY STATEMENT OF  
MERCK & CO., INC.  
IN  
RESPONSE TO PORTIONS OF TESTIMONY BY  
WILLIAM M. O'BRIEN, M.D.,  
ASSOCIATE PROFESSOR OF PREVENTIVE AND  
INTERNAL MEDICINE, UNIVERSITY OF  
VIRGINIA SCHOOL OF MEDICINE  
TUESDAY, APRIL 23, 1968  
BEFORE  
THE MONOPOLY SUBCOMMITTEE  
SENATE SELECT COMMITTEE ON SMALL BUSINESS**

This statement is filed pursuant to permission granted by the Chairman of the Subcommittee to comment on testimony by witnesses who appeared before the Subcommittee on April 23 and 24 and May 1 and 2 with regard to this Company's performance in the development and marketing of its product 'Indocin'. This supplementary statement covers two points.

(a) Dr. O'Brien was permitted, at the Committee's request, to review Merck's indomethacin New Drug Application file at the Food and Drug Administration, including FDA's internal memoranda relating to the application. Dr. O'Brien quoted extensively from a January 25, 1967, memorandum of David Hurwitz, M.D., of the Food and Drug Administration. (Pages 4538-40) Dr. O'Brien failed to mention that the document quoted from was primarily concerned with a review by Dr. Hurwitz of a supplement to the original New Drug Application, filed in May 1966 to cover additional indications. Dr. O'Brien quotes the document as if it dealt only with the approval of the original New Drug Application.

As Dr. Hodges pointed out in his testimony (pp. 4668-70), Dr. O'Brien also appears to have overlooked a subsequent memorandum of Dr. Hurwitz dated August 1967, in which he, after further review of the data, substantially revised the opinions expressed in his memorandum of January 25, 1967. We have appended to this statement a copy of Dr. Hurwitz's August 1967 memorandum, and request that it be placed in the record at this point.

(b) In his testimony on April 23, Dr. O'Brien appeared to cast doubt on the integrity and reliability of clinical investigators selected by Merck and other pharmaceutical companies, and on the method of their selection.

To complete your record, we are setting forth below Merck's policy and procedure in the selection of investigators. (Copies of this statement were, at the request of the Subcommittee staff, submitted prior to Merck's appearance on May 3, 1968, but were not made a part of the record.)

**MERCK'S POLICY AND PROCEDURE IN THE SELECTION OF INVESTIGATORS**

After careful review of preclinical evidence of safety and pharmacological activity of a new therapeutic compound, it may be cleared for clinical study. The Company's medical and scientific staff then must decide whether they wish to carry the compound into the clinical investigative process. If they do, a plan for

the clinical program is developed and the clinical objectives—based on the pharmacological and toxicological data derived from animal studies—are established.

Clinical protocols are then prepared. These outline the broad design of the proposed clinical studies and convey the basic information on toxicology and pharmacology with which clinical investigators must be familiar in order to study the drug in man. In developing the protocols, we consult with clinical pharmacologists, biostatisticians, and selected investigators. In this process, we strive for the best possible study design, reconizing at the same time that the new drug can only be studied within the scope of presently available methodology as well as the availability of patients, volunteers, and clinical research facilities.

Once the clinical plan has been completed and submitted to the FDA, clinical studies are initiated in Phase I—which probes the basic pharmacology and metabolism of the drug in man. These studies are carried out only by expert clinical investigators in a few selected clinical laboratories, normally not more than five. These are almost always in university-affiliated medical centers and are carried out in carefully selected individuals.

If Phase I studies provide evidence of safety and pharmacological activity, the clinical program is expanded to include a half dozen or more expert investigators in the field of medicine where the drug promises to be useful (Phase II). An antihypertensive drug, for example, is taken to specialists in cardiology who have had experience in the investigation of such drugs.

By this time the appropriate dosage range for the drug is fairly well established, and the effects of the drug can be studied in various disease states where it is expected to have a beneficial effect. This additional experience, involving studies in depth, adds greater assurance of safety and efficacy and provides the basis for expansion of the studies into Phase III.

The final phase (III) provides still greater evidence of safety and therapeutic benefit which can then be well delineated in the clinical indications for use of the drug. These studies are carried out by carefully selected physicians experienced in the field of study concerned. These are selected by our medical staff based upon knowledge of their prior work in the field, their prior work for us, and in some instances on the recommendation of Phase I and II investigators. A primary purpose is to obtain a deeper insight into how the drug will respond in the hands of physicians generally.

During all three phases, the studies are well controlled. The more sophisticated and complex double-blind studies are undertaken particularly during the Phase III stage. These studies serve as much as possible to eliminate bias and the elusive clinical variables which are ever present. It must be recognized, however, that although data from such studies tend to appear more convincing, their validity may also be subject to question. In most fields of medicine, it has yet to be proved that *all* relevant factors have been accounted for in the control design, and thus we must avoid total reliance on what may be simply a tidier version of an imprecise appraisal of a drug.

The first and ultimate responsibility for drawing conclusions with regard to safety and efficacy of a drug lies within the medical staff and the research organization of the Company sponsoring the studies. We do not and cannot delegate this responsibility to a third party.

Financial assistance in the form of grants-in-aid is given to the investigator to cover the expenses incurred in carrying out his research. For the most part a contractual relationship is established between the Company and the university or institution where the work is being carried out. Grants are made on a sound budgeting basis. Clinical research grants are never based on the condition that a certain number of case reports be submitted or that only positive data be provided. Our records clearly show that studies supported by grants frequently fail to support the objectives set forth in the clinical protocol, either because of a shortcoming in the drug itself or failure to anticipate one or more of the numerous variables which arise during the clinical study and result in negative data.

Most grants-in-aid cover the following costs: Laboratory, technical, clerical, hospital, and bed costs; supplies, materials, and overhead. If there are indirect costs assigned to a project as part of the investigator's overall research budget, these too are covered. Should the investigator request that special studies be done—such as radioisotope work, or metabolic balance studies demanding the special facilities of metabolic ward—these are financed to cover all direct and indirect costs.

It is difficult to generalize about the costs of clinical research in the conduct of studies with new drugs. One cannot, for example, correlate the number of

patients or case reports per study with the cost. Where a minimum amount of laboratory work is required and the patients may not be seen by the physician more than three or four times during the course of the study, the cost of studying 50 patients may not be more than \$5,000. On the other hand, studying six patients for six weeks in the hospital or in a metabolic ward, at the rate of possibly \$100 a day, may cost \$25,000 or more. Costs vary with the degree of patient or hospital care needed, the extent of laboratory work, and the number of individual technical or professional tests to be done.

Today, when hospital, laboratory, and research costs are skyrocketing, and when the expense of conducting clinical research on a new drug may extend over a period of three to five or more years, the cost of clinical investigation has become substantial. Indomethacin studies extended over a period of three and one-half years, from November 1961 to NDA approval in June 1965—and indeed a large program still continues.

It is rare for a clinical research program involving a new drug to cost less than a half million dollars. Most are closer to one million dollars before an NDA has been achieved. Even after NDA approval, there are aspects of clinical research which may be pursued for years thereafter.

It should be pointed out that a sponsor would be foolish—in this developing age of clinical science—to undertake to "pay" an investigator for positive data which cannot be substantiated. This could not be done with responsible clinicians. In any case, the cost of conducting medical research is already so high that to add a factor of cost to this by trying to buy data which could not be confirmed would be not only bad ethics and bad research but also bad business. A well-established research enterprise such as ours, with its scientific and medical reputation at stake and investing very heavily in obtaining clinical data, has much more to lose than to gain from this inaccurate data.

It is the policy of the Company to seek out the best and most experienced clinical investigators it can find to evaluate its new drugs or to explore new uses of existing drugs. In 1967, we invested to \$2,000,000 in the clinical investigative phase of our research effort, supporting the work of several hundred investigators here and abroad. Although averages are not always meaningful or as accurate as one might wish in describing such a program, we estimate our "average" clinical research grant to have been approximately \$5,000 during 1967.

This compares with the average for an NIH clinical grant of perhaps \$15-25,000 during the same year . . . it is recognized, of course, that the NIH grants are more broadly based and for a longer term. But there are other comparisons that can be made with NIH grants as well. Like the NIH grantee, the Merck grantee is free to and encouraged to publish his data, whatever they may be. Like the NIH grantee, the Merck grantee is committed only to the accomplishment of a study, not to results. Like the NIH grantee, the Merck grantee is drawn from a cross-section of the nation's and the world's resources in the health sciences. The excellence of the performance and the quality of the data depend not so much on the sponsoring institution as on the state of the art and the state of the science in a given field. Thus, clinical research supported by Merck is and will be qualitatively similar to research supported by Federal funds. At the same time, both companies such as Merck and Federal agencies such as NIH have a responsibility to do what they can to help strengthen the resources for better and ever better research, including clinical research.

The key thing, from the Company's point of view, and the key message it would wish to communicate to a Committee of Congress that has interested itself in this question, is that the objective of the Company is quality performance in clinical research yielding reliable data. This represents an ever-present goal. We do not suggest that we are universally successful in achieving this goal; to attain such a level in any human endeavor is perhaps impossible. But our record has been good.

Indeed, there is no other course for a responsible company to take. We are dealing with products related intimately to man's aspiration for health and freedom from pain and suffering. All such products have a great capacity for good or for harm. In the final analysis, we are responsible for our drugs and have nothing to gain and everything to lose by performing inadequately in our own laboratories, or by permitting sloppy performance by outside investigators, or by knowingly—in our evaluation of preclinical and clinical data—ignoring and neglecting the facts as they bear on the safety and effectiveness of a new drug.

[Copy made by Merck from facsimile]

## INDOCIN IN RHEUMATOID ARTHRITIS

(By David Hurwitz, M.D., Metabolic &amp; Endocrine Div./ODS)

Since its introduction in March of 1965, Indocin has enjoyed wide public acceptance as an anti-arthritis agent. Early pharmacologic studies had indicated an unprecedented potency when the drug was used to control inflammation in various animal models. It was hoped, at that time, that Indocin would have a high therapeutic ratio and thus offer a significant advantage over corticosteroids with their multiplicity of serious adverse reactions. Unfortunately Indocin has shown a similar propensity to cause a wide variety of serious and sometimes fatal reactions, and its clinical usefulness has been limited by its toxicity. This toxicity has been well documented and is now well-appreciated by the medical profession, and Indocin has taken its place along side aspirin and phenylbutazone as another useful agent in a group of poorly understood diseases not amenable to any definitive therapy.

At no time, however, was the actual efficacy of Indocin questioned. It was appreciated that the drug worked considerably better in acute inflammatory conditions like gout than in the chronic arthritides such as rheumatoid arthritis, but the drug was believed efficacious in the latter condition. Several new studies published in the first quarter of 1967 in major scientific and medical journals now dispute the usefulness of this drug in rheumatoid arthritis. Chief among them in an exhaustive clinical study carried out by the Cooperating Clinics Committee of the American Rheumatism Association in association with Dr. Donald Mainland, a well-known biostatistician. This exhaustive study involved 141 patients treated for a three-month period and required ten months to be completed. Indomethacin was compared in a double-blind fashion with a placebo, the patients being allowed free use of aspirin as needed. Although many different parameters were measured and studied by sophisticated statistical techniques, the authors were unable to find any statistically significant differences in those parameters between Indocin and the placebo medication.

In the same month, Donnelley et al. published a similar study in the British Medical Journal. The British authors used a double-blind crossover study comparing Indocin with a placebo, and they also were unable to establish any statistically significant difference between Indocin and placebo. In neither study were there any serious reactions to the medications.

In a third article by Pinals and Frank no differences was found between Indomethacin and aspirin in the treatment of rheumatoid arthritis. This study was a double-blind crossover type and was not as thorough or as well planned as the previous two studies. The authors arrived at the conclusion that Indocin and aspirin have no significantly different effect on the parameters measured which is justified by the results of the experiment, but they seem to have missed the obvious conclusion that no therapeutic effect was demonstrated for either of the medications. The measured parameter, while not varying significantly between the Indocin-treated group and the aspirin treated group, also did not vary significantly within each group at two weeks and four weeks. The lack of inclusion of base line data adds a further difficulty to the interpretation of this paper. In contrast to this study, however, the Mainland and the Donnelly studies were well-planned, well-controlled, and seemed to be products of rigorous, thoughtful research.

Indocin's potential toxicity would make its use in rheumatoid arthritis unacceptable if indeed it has no efficacy for this condition. Therefore it was deemed necessary to review the original studies establishing efficacy in this disease. A search of 100 volumes of the NDA revealed six acceptable controlled studies, five of them double-blind the other single-blind. All of these studies claimed efficacy for Indocin but they vary in quality. As a whole, they would seem to indicate efficacy in this condition; results are summarized in the table, below.

In comparing the old studies to the new ones, it is obvious the latter are better-controlled and use more sophisticated methods of evaluation. Because of the extremely variable nature of the disease and the consequent difficulty in evaluating modes of therapy, it is impossible to say that the new studies outweigh the old, particularly in view of the large mass of testimonial data indicating efficacy. While testimonial studies are not in themselves adequate to allow approval of a drug by the FDA, they certainly cannot be disregarded as meaningless when the ultimate usefulness of the drug and its success is determined by individual

patient reaction to the medication. We are therefore faced with the dilemma of a drug whose efficacy has been seriously questioned by excellent studies but which enjoys solid acceptance by the medical community and the patients it treats. At the present time, then, it would seem wise to consider Indocin as probably effective in rheumatoid arthritis pending further studies in this area. The drug is at the present time safe for use in this condition since in the dosages commonly employed there is very little risk of a serious adverse reaction. This author has recommended in the summary of the most recent supplement submitted by Merck, Sharp & Dohme that further studies be carried out to determine the efficacy of Indocin in rheumatoid arthritis.

TABLE I.—INDOCIN REVIEW—CONTROLLED BLIND STUDIES FROM ORIGINAL NDA

Author	Date	Volume	Number of patients	Type	Results	Comment
Hart, F. D., and Boardman, P. L. (British Medical Journal, 11:1281, 1965).	1965	30	18	Double-blind crossover comparison with Phenylbutazone 56 days.	(1) Little difference between drugs in therapeutic or adverse effects; (2) Indocin had greater effect on reduction of joint swelling; (3) no serious reactions.	Data incomplete as regards grip measurement or preference, it would be desirable to see how parameters were measured and actual figures; without these we are unable to tell if the patients improved.
Percy, J. S., Stephenson, P., Thompson, M. (Ann. Rheum. Dis.) (23:226, May 1964).	1964	30	24	Double-blind crossover sequential comparison with Phenylbutazone.	(1) No significant difference between drugs in patient preference or grip strength; (2) Phenylbutazone had lower incidence of adverse reactions (none serious in either group).	The ARA Committee has noticed a feeling of well-being in patients on Indocin; is this the case here? No objective benefit was noted in the single measured parameter—grip strength.
Wenka, J., Jones, L., Wood, P., Dixon, A.	1964	30	22	Double-blind crossover comparison with placebo 6 weeks.	(1) Patients preferred Indocin but no measurable difference in grip strength; (2) no significant reactions.	Results variable, uncontrolled use of aspirin and prednisone in study No. 1, make it invalid. (2) data scan, inadequate placebo effect (nil); validity of statistics, questionable dosage of other medications unspecified (Study No. 2).
Ward, J. R.	1965	30	Studies: (1) 29; (2) 40.	2 studies double-blind crossover comparison with placebo. In study No. 1, unlimited and irregular use of aspirin and steroids was permitted. Study No. 2, all patients on fixed aspirin and prednisone, dosage 4 months.	(1) Indocin group had less tenderness and morning stiffness; (2) Indocin group had significant decrease in pain, morning stiffness, swelling, tenderness; (3) no significant reactions.	(1) Well-developed response criteria; (2) large, unwieldy amount of data; (3) poorly controlled, variable dosage and length of administration; (4) results only suggestive to efficacy.
Smyth, C. J.	1965	47	55	Single-blind variable time several weeks to several months.	Indocin effective in several parameters as compared to placebo.	(1) Did patients use other medications during this long study?
Bode, J. J.		80	27 total, 15 on Indocin.	Double-blind 3 months.	(1) Indocin group had decrease joint tenderness and pain, no difference in parameters; (2) no serious reactions.	(1) No difference between Indocin and aspirin 2 months.

TABLE II.—INDOCIN—NEW STUDIES QUESTIONING EFFICACY

Pinis, R. S., Frank, S. (NEJM March).	1967	—	24	Double-blind crossover comparison with aspirin 2 months.	(1) No difference between Indocin and aspirin; (2) no serious reactions.	(1) No baseline data; (2) neither drug had any clinical effect which makes results difficult to interpret; authors did not discuss this point; (3) 5 patients on steroids.
Donnelly, P. Lloyd, K., Campbell, H. (British Medical Journal, January 1967).	1967	—	30	Double-blind crossover comparison with placebo 1 month.	(1) No statistical significant difference between Indocin and placebo; (2) some delay in onset of lagtime on Indocin but not statistically significant; (3) no serious reactions.	(1) Well-designed study, well-controlled; (2) used aspirin in all patients but amount was recorded and evaluated statistically.
Mainland et al. (Clin. Pharm. and Therapeutics, January 1967).	1967	—	141	Double-blind comparison with placebo 3 months.	(1) No statistically significant difference between Indocin and placebo; (2) no serious reactions.	Use of aspirin reduces sensitivity of experiment and may mask small differences between placebo and Indocin.

SUPPLEMENTARY STATEMENT OF  
MERCK & CO., INC.  
IN  
RESPONSE TO PORTIONS OF TESTIMONY BY  
JOHN JENNINGS, M.D., ACTING DIRECTOR,  
OFFICE OF MARKETED DRUGS, BUREAU OF MEDICINE  
FOOD AND DRUG ADMINISTRATION,  
GIVEN ON  
WEDNESDAY, MAY 1, 1968  
BEFORE  
THE MONOPOLY SUBCOMMITTEE  
SENATE SELECT COMMITTEE ON SMALL BUSINESS

This statement is filed pursuant to permission granted Merck by the Chairman of the Subcommittee to comment on testimony by witnesses who appeared before the Subcommittee on April 23 and 24 and May 1 and 2 during hearings inquiring into this Company's performance in the development and marketing of its product "Indocin".

On May 1, Dr. Jennings, testifying for the Food and Drug Administration, described the negotiations between the Agency and the Company that led to two package circular revisions in the fall of 1966. (Pages 4690-4704) The general impression we receive from Dr. Jennings' testimony is that the Food and Drug Administration tried from July 15 forward to get the Company to add additional warnings, contraindications, and adverse reactions to the package circulars on "Indocin", but that the Company was reluctant, even recalcitrant, in doing so. It is implied that the Company should have voluntarily made the requested changes long before it did so. Thus, "By regulation, these changes could and should have been put into effect by the firm at the earliest possible times, without awaiting approval from the FDA." (Page 4690)

On the other hand, there is in the same testimony an implied criticism of the Company for proceeding voluntarily without FDA approval when it did change the package circular. "Rather than wait for all the recommended labeling changes to be worked out with us, interim revisions of the labeling were put into effect by the company without our advance approval." (Page 4694)

Dr. Jennings concludes that our letter to doctors transmitting the volunteered package insert changes was "promotional literature" in which the original intent to war physicians of additional hazards was "completely lost." (Page 4695)

His concluding testimony on this subject could leave the impression that the Agency was struggling with the massive problem of a recalcitrant firm unwilling to convey to the doctor important new information on hazards of its drug.

This impression is not justified by the actual facts. We submit below a brief review of our communications with the Food and Drug Administration during the spring and summer of 1966 on revisions in the package insert for "Indocin." These are summarized from our internal memos and records of correspondence with the Agency.

1. *April 6, 1966.* Telephone call to our Dr. Shaffer from Dr. O'Grady, FDA investigational Drug Branch. This call dealt with the Company's IND on "Indocin" covering studies in indications not in the then-approved NDA. Dr. O'Grady reported that the Adverse Reaction Bureau, FDA Bureau of Medicine, thought there was an increasing number of side effects associated with the use of "Indocin". Dr. Shaffer told Dr. O'Grady that from our review of reported adverse reactions, the incidence of such reactions was not increasing but decreasing with more widespread use of the drug. A request was made to discuss the entire investigational program with Dr. O'Grady.

2. *April 7, 1966.* Dr. Shaffer telephoned Dr. O'Grady for a date for conference. This was tentatively set for April 15, but later in the day changed to April 18. FDA was asked whether it had adverse reaction data from sources independent of Merck.

3. *April 19, 1966.* Conference between FDA and Company medical representatives. Although the conference related primarily to the investigational studies for added claims, the FDA representatives reported their opinion that the current package insert should be revised to reflect current adverse information reports, including some data they had that we did not have. The Company medical representatives felt Merck should make a complete review of the labeling and

see whether the data available to us suggested the need for package circular revisions.

4. May 2, 1966. As a follow-up to the April 19 conference our Dr. Shaffer telephoned Dr. Seife and asked if he would provide us with the type and number of adverse information reports they had received through the FDA Adverse Reaction Reporting Program. Dr. Seife called back the same day and gave us this information, characterizing the reports with regard to the role "Indocin" may have played. He promised to keep us informed as additional reports came in to FDA.

5. May 5, 1966. Letter from Dr. Ruskin of the FDA Division of New Drugs, primarily relating to the pending NDA on an "Indocin" formulation. It "recommended that revised labeling be submitted supplemental to your approved application for the capsule form to contain the most recent reports of adverse reactions which are not in the current labeling. . ." In this letter Dr. Ruskin requested that a statement be added in boldface type to the warning section of the labeling that this was "not an innocuous drug," and should not be used for other than recommended indications, and not be used in women of childbearing age. "*We recommend that these labeling revisions be discussed with the New Drug Surveillance Branch. . .*" (Italic added.)

6. May 27, 1966. Our Dr. Shaffer telephoned Dr. Seife of the New Drug Surveillance Branch to arrange for the requested discussion. We suggested a meeting on June 6, but Dr. Seife was "occupied with another problem" and said he "would like to arrange for such a conference before the end of June." It was left that Dr. Seife would let us know when he was available. Additional adverse information FDA had received from March 24 through May 5 was communicated in this conversation.

7. July 1, 1966. Our Dr. Shaffer telephoned Dr. Seife of FDA to ask about the proposed meeting. Dr. Shaffer learned that Dr. Seife was "out of town" and that Dr. Jennings, Acting Director of the Drug Surveillance Branch, should be called.

Dr. Shaffer called Dr. Jennings and learned that the matter had been reassigned to him. He said he would discuss with Dr. Ruskin the May 5 letter we had from Dr. Ruskin, but that if any *urgent changes in labeling were necessary*, these could be made without submitting a new drug application supplement for FDA approval. Dr. Shaffer told Dr. Jennings that "*in order to avoid subsequent changes requiring reprinting etc., we requested an opportunity to discuss labeling revisions with them as requested by the Ruskin letter of May 5, 1966.*"

Dr. Jennings asked that we "check back with him in about one week."

8. July 15, 1966. Conference in Washington between FDA and Company medical representatives. Dr. Seife was to enter the hospital for surgery and our labeling matter had been assigned to Dr. Standard.

A summary of major labeling changes prepared by Dr. Seife was reviewed in detail. Dr. Seife told us *the recommendations outlined during this discussion would be sent to us in the form of a letter.*

9. August 4, 1966. Dr. Shaffer wrote to Dr. Jennings as follows:

"As you know, we met with Dr. Seife, Dr. Bryan, and Dr. Standard July 15 to discuss proposed revisions of the 'Indocin' Package and Direction Circulars. It was our understanding that Dr. Seife's proposed revisions would be submitted to us by letter. *We would appreciate receiving this communication so we may prepare an appropriate revision based both upon your proposals and our evaluation of the available data.*" (Italic added)

10. August 22, 1966. No further communication from FDA had been received. On this date, the Merck Sharp & Dohme Division Counsel advised that, since we were willing to accept a number of the FDA recommended changes, we should make the changes voluntarily, notify the FDA, and mail the revised circular to physicians.

11. September 2, 1966. We submitted a supplemental NDA containing the added contraindications, precautions, and adverse reaction information, stating in the transmittal letter to the FDA: "We feel it important that these changes be placed into effect at the earliest possible time." The majority of the FDA's suggestions were adopted. We gave our reasons in that letter for not adopting all of them.

Our letter ended with the following paragraph:

"We appreciated the opportunity to discuss suggested changes in the Indocin labeling with your staff. We believe that the revised labeling submitted with this supplemental application accomplishes the mutual goal of providing the physician with the most useful information about this drug. To accomplish this goal, we have taken the position that the labeling should be unencumbered by a listing of

every report of an adverse reaction if, in our best judgment, there does not appear to be a reasonable relationship to the drug. An attempt has been made to provide the physician with some guidance as to the relative frequency with which the listed adverse reactions may occur. We are following the clinical experience with this drug closely and will make further labeling revision if and when indicated."

12. September 30-October 6, 1966. No reply to our September 2 letter had been received from the Food and Drug Administration. On September 30, we started our mailing to doctors, and on October 6 notified the FDA that the revised circular had "just been mailed." Enclosed in the letter was the circular, the transmittal letter and the envelope which contained in large red letters, "Do Not Discard Before Reading—Drug Safety Information." The revisions were noted in boldface type so that they would not be missed by the readers.

Although the letter sent out to doctors was clearly marked as noted above, and the enclosed revised insert was made easy for the physician to read, and the body of the letter conveyed what it was intended to convey, it did contain first and last sentences that tended to give it a promotional overtone. In retrospect, we think it should not have had those sentences in it. We do not do everything perfectly, and did not do so here. Nevertheless, we think that the essential intent and message of the letter was clear, and that Dr. Jennings' categorical opinion that original intent was "completely lost" (page 4695) is overstated.

During the course of these discussions with the FDA, we found ourselves involved in differences of medical opinion about the implications of the reports of adverse reactions and side effects of the drug. In terms of telling physicians about them, we were of the opinion that placing before them a mass of detail, much of it repetitious, would tend to obscure the really important warnings. As to the reports themselves and their significance, there were not unnatural differences of opinion. Our medical staff felt, and still does, that nothing essentially new was emerging from these reports, that the increasing number of reported reactions reflected the increasing use of the drug rather than an increasing incidence of reactions, and that as more experience was gained what was emerging was an expected refinement of the original essential pharmacologic profile. The Food and Drug Administration people appeared to think differently. It did not—and does not now—follow that they were right in this opinion.

A good example of this difference of opinion is our view of the value and proper use of the drug in cases of juvenile rheumatoid arthritis. Dr. Jennings, during his testimony, refers to reports of deaths in children associated with the use of indomethacin. He disposes of a number of these cases as probably not due to the drug, but reserves opinion as to several. There is a considerable difference between a drug's being possibly linked to a death, and definitely related to it. The FDA is understandably cautious and has consistently singled out pediatric age groups as a patient population bearing risks beyond the adult group.

From the beginning, because the FDA did not accept our pediatric data, our domestic package circular included a specific contraindication against the use of 'Indocin' in children of pediatric ages.

During our discussions with the FDA in the spring and summer of 1966 about the revision of our labeling, the FDA itself *did not request us* to include any statement in the circular referring to fatalities in children. The only difference between us at that time was whether the existing contraindication of 'Indocin' for children was sufficient, or whether it should be strengthened by the addition of a phrase at the beginning of the circular stating "Not for Use in Children."

We did not believe then and we do not believe now that this addition was necessary or desirable. In the light of the FDA's desire for more emphasis, we did italicize the portion of the circular containing the specific contraindication for use in children, so that it would come even more prominently to the attention of doctors. Moreover, we added an additional paragraph, printed in boldface type in the revised circular, calling attention to the fact that 'Indocin' could mask the existence of infection and reminding physicians that it should be used with caution in patients with existing infections. In our scientific opinion, the reported deaths in children were related more to the existing complications of a serious infection in these patients than to the fact that they were children.

FDA insisted in meetings that followed the events summarized above that we make a further amendment adding a specific statement at the beginning of the circular that the drug should not be prescribed for children, and it requested for the first time that we refer in the contraindications to reports of severe reactions, including fatalities, in a few cases of severe juvenile rheumatoid arthritis.

Although we did not agree with this medical judgment, we did include these statements because of the FDA's insistence.

In the judgment of our medical staff, the total prohibition of 'Indocin' in juveniles suffering from acute rheumatoid arthritis is not warranted. Acute juvenile rheumatoid arthritis is a serious and often hopeless disease. If treated with corticosteroids, very serious effects—including loss of calcium in the bones and the disturbance of the endocrine system—can frequently result. In those children who do not respond to aspirin or cannot tolerate it, we believe it is medically preferable to treat them with 'Indocin' than to risk corticosteroids or to leave them untreated. The FDA does not agree with us, and for that reason we have always contraindicated 'Indocin' for this purpose in the United States. But many doctors do administer the drug successfully to children in Europe. The matter presents a question of refined medical judgment, but it is one on which you will find much responsible opinion on our side.

It must be accepted as a truism that the FDA is at all times in a position to bring great pressure on us to adopt every detail of what they want. For our part, we wish to cooperate as much as possible with the Agency. Good relations with it are essential for us.

Subsequently, when at Dr. Goddard's request we met on November 11, 1966, with him and his staff to discuss our labeling and advertising of 'Indochin', we reviewed the differences of opinion about the controversial points and the transmittal letter to doctors. As a result of the meeting, even though our respective medical staffs continued to be in disagreement on a number of issues, we chose to abide by FDA's wishes and sent out a further revised circular containing all the changes FDA requested, including the different typographical and position treatment of the contraindications in children. This revised circular was transmitted to doctors in December, 1966, with a letter which made reference to nothing but the changes in the insert. Both the circular and the letter were worked out with the FDA.

Neither in these meetings nor subsequently was there any recalcitrance on our part. In our opinion, sincere disagreements in medical opinion cannot be equated with recalcitrance. We were deeply concerned at the time at what seemed to be imputations to us of bad motives and lack of integrity. We argued against such imputations most vehemently. But we worked out this particular problem on the basis of a full and frank discussion of where we and they stood on the matter.

Perhaps it is fair to say that the Company and the FDA must share the responsibility for the time it took to issue the first revised circular. The job could have been done faster if we and the FDA officials concerned had been able to arrange more frequent meetings and to obtain prompt decisions. With respect to the wording of the first transmittal letter to doctors, we must and do accept sole responsibility.

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**SUPPLEMENTARY STATEMENT OF  
MERCK & CO., INC.  
IN  
RESPONSE TO PORTIONS OF TESTIMONY BY  
ROBERT S. McCLEERY, M.D., ACTING DIRECTOR  
DIVISION OF MEDICAL ADVERTISING, BUREAU OF MEDICINE  
FOOD AND DRUG ADMINISTRATION  
GIVEN ON  
THURSDAY, MAY 2, 1968  
BEFORE  
THE MONOPOLY SUBCOMMITTEE  
SENATE SELECT COMMITTEE ON SMALL BUSINESS**

This statement is filed pursuant to permission granted Merck by the Chairman of the Subcommittee to comment on testimony by witnesses who appeared before the Subcommittee on April 23 and 24 and May 1 and 2 during hearings inquiring into this Company's performance in the development and marketing of its product, 'Indocin'. This supplementary statement covers portions of the testimony of Dr. McCleery on May 2.

We do not agree with the allegations of fact, charges, and conclusions contained in Dr. McCleery's testimony on a number of detailed aspects of our advertising of 'Indocin', such as his extensive discussion of the reference in our advertisement to an article by Hart and Boardman in the *British Medical Journal* of October 18, 1963. We have presented to the Food and Drug Administration detailed factual and legal responses to these charges. In our view, the advertising statements the Company used did not misrepresent the status of the drug, intentionally or otherwise. In any event, the criticized statements have not appeared in any Merck advertisement since 1966.

As Mr. Goodrich testified before your Subcommittee, this matter is now pending before him for a decision on whether further legal proceedings should be recommended. While the matter is in this status—and since the issues involved require lengthy analysis and interpretation of the criticized quotations, the scientific data on which they were based, and the articles from which they were taken—we believe it would be inappropriate to comment on the issues in this forum.

We do feel, however, that we should note our exception to one specific point about our advertising raised by Dr. McCleery, since it suggests knowing misrepresentation on our part. In commenting on an advertisement in the July 18, 1966, edition of the *Journal of the American Medical Association*, he said that the advertisement ". . . featured the claim of one of the participants in a Merck-sponsored symposium. This is attributed to Dr. Englund—they featured a claim, quoting from him at this symposium that [he] had had 500 patients on the drug for three years, when Merck's own records would have told them this was not true." (Page 4733)

The advertising to which he referred contained this statement:

"I have had some 500 patients on indomethacin now for about three years. I find it an extremely helpful drug. I think there are certain areas where it will be without question [a] drug of choice. One of these is osteoarthritis of the hip."

This quotation was taken from a statement made by Dr. DeWitt W. Englund in response to a question from the chairman of an international symposium on Non-Steroidal Anti-Inflammatory Drug Therapy in Rheumatic Diseases conducted September 26-28, 1965, in New York City, by the Excerpta Medica Foundation.

We do not believe that Dr. McCleery's criticism of the Company for using the statement "when Merck's own records would have told them this was not true" is warranted. Merck could properly have relied on Dr. Englund's recorded and published statement as the factual observation of an eminent and leading rheumatologist. Our records did show that Dr. Englund had treated at least 500 patients by that time. The information was contained in Merck's first quarterly report to the FDA after the approval of the New Drug Application on June 10, 1965. It was sent to the Agency about the middle of September, 1965, and should also be in its records.

In another portion of his testimony, Dr. McCleery described his understanding of our connection with a lay article about the drug in *Pageant* magazine. (Pages 4716-20) We consider this also to be fundamental because, according to Dr. McCleery, it led the FDA to conclude that this Company "might not be scrupulous in its advertising to the medical profession."

We are therefore setting forth in detail what took place with regard to the *Pageant* article:

1. On February 15, 1966, Mr. Robert P. Goldman, who has been a science writer since the late 1940's, telephoned John E. Fletcher, Director of Public Relations for Merck, stating that while in France his wife had been given a prescription for "Indocin" for the treatment of tennis elbow. Mrs. Goldman and her doctor felt that the treatment had been successful. When Mr. Goldman inquired of the doctor as to the source of the drug, he was surprised to learn that it had been originated by an American company, namely Merck. Mr. Goldman chided Mr. Fletcher about the fact that there had been no publicity about the drug. He said he planned to write an article about indomethacin and asked the company to provide him with some background material on it.

2. On February 17, 1966, Mr. M. T. Noar, a member of the Company's public relations staff, at the request of Mr. Fletcher, sent Mr. Goldman appropriate background information, including a "background" containing medically and scientifically authenticated information about the drug, its genesis, and the disease conditions for which it is approved; a package circular; relevant papers by scientists from Merck and other laboratories; and a bibliography.

3. Sometime within the next month, Mr. Goldman called Mr. Fletcher stating that he would like to have some human interest stories to increase readability

and asked whether we had any letters. Mr. Noar, at Mr. Fletcher's request, sent Mr. Goldman six letters from patients who had voluntarily written to the Company. Identification of the individuals and their physicians was blocked out in the copies sent to Mr. Goldman.

a. The first letter, dated August 1965 from San Diego, California, dealt with osteoarthritis of the hip joint (an approved claim).

b. The second letter, dated December 14, 1965, related in the patient's language to arthritis (there was no reason to suppose it other than rheumatoid—an approved claim).

c. The third letter, dated December 24, 1965, from Morganton, North Carolina, related to osteoarthritis of the hip (an approved claim).

d. The fourth letter, dated January 6, 1966, from Williamstown, Massachusetts, related in the patient's language to arthritis (there was no reason to suppose it other than rheumatoid—an approved claim).

e. The fifth letter, dated January 10, 1966, on the letterhead of the Enterprise City School District, related to rheumatoid arthritis (an approved claim).

f. The sixth letter, dated October 4, 1965, contained the following paragraph: "I am not too sure whether I have bursitis, tendonitis, or just plain arthritis, and also, my doctors don't know. However, I do know that I had to give up playing golf and I do know that after these few days that I have been taking your wonderful capsules, that I am going to play golf again, and soon."

4. On April 14, 1965, Mr. Goldman wrote Mr. Fletcher stating that he had done the piece on 'Indocin' and that it would probably appear in *Pageant* in July, with the magazine to be on the stands about June 16, 1966. According to his records, Mr. Fletcher also received a telephone call in mid-May from Mr. Goldman in which the latter said that he thought his story would appear in a summer issue of *Pageant*.

5. On the morning of June 15, 1966, while driving to work, a member of the Company's public relations staff heard a radio commercial about a story on 'Indocin' in *Pageant*. He stopped by a newsstand and purchased the magazine in which the article appeared. This was the first time anyone from the Company had seen it.

6. On June 21, 1966, a copy of the article was sent to Mr. Cron, then Director of Public Information and Education of the Food and Drug Administration, together with a copy of an internal memorandum explaining the article's origin.

7. Nothing was heard from the FDA about the article or our part in it until a speech was delivered by Mr. William W. Goodrich, Assistant General Counsel of the Food and Drug Administration, before the Pharmaceutical Advertising Club in New York on October 20, 1966, in which he criticized the *Pageant* article and gave his version of the Company's role in it.

This chronology of events demonstrates that:

1. The Company did not stimulate or cause publication of the article; it responded to a request for information from a recognized science writer.

2. Approved claims were named in all of the letters supplied to Mr. Goldman by Merck. No case histories on unapproved claims were submitted. No testimonials on unapproved claims were submitted. In one single letter the patient reported that he and his doctors did not know whether he had tendonitis, bursitis, or arthritis—arthritis being an approved claim.

3. Merck did not see the text of the article before it appeared in print; it first saw the article when the July issue was purchased from a newsstand on June 15, 1966.

4. Analysis of the article shows that, of the nine personal experiences recited by the authors, only four are attributable to the Company. Of these four, three involve approved claims only. The fourth mentions "bursitis." Although the article purports to quote extracts from this fourth letter, the quotations are not accurate and they changed the letter's meaning by omitting the reference to arthritis, an approved claim.

5. The Company voluntarily made the facts known to the FDA shortly after the published article came into Merck's hands.

6. The FDA did not discuss the *Pageant* article with Merck or seek to verify Merck's role with respect to it prior to the time Mr. Goodrich made a public speech attacking the article and the Company on October 20, 1966.

Senator NELSON. If you have a supplementary comment, it will be printed in the record at the appropriate place.

Mr. GADSDEN. Thank you.

(The subsequent correspondence and statement of Senator Scott follows:)

U.S. SENATE,  
COMMITTEE ON THE JUDICIARY,  
Washington, D.C., May 9, 1968.

Hon. GAYLORD NELSON,  
*U.S. Senate, Washington, D.C.*

DEAR GAYLORD: You will recall that at the Monopoly Subcommittee hearing of Friday, May 3rd you granted me permission to submit a statement at the end of that day's hearings.

A copy of that statement is enclosed.

I would like to have it printed in the permanent record of the hearing of May 3, as if delivered personally, immediately following Mr. Gadsden's final remarks and just prior to your statement recessing the hearing.

Cordially,

HUGH SCOTT, U.S. Senator.

**STATEMENT OF HON. HUGH SCOTT, A U.S. SENATOR FROM THE STATE OF  
PENNSYLVANIA**

Mr. Chairman, it is entirely clear that today's hearings, requested by Merck & Co., have provided a substantial step forward in dispelling the pall of confusion that has accumulated on these issues during the last two weeks. The value of taking testimony from the party most directly involved in a problem was demonstrated today.

The testimony indicates that there is essentially no problem regarding the safety and effectiveness of this drug as it has been determined by a broad group of highly qualified experts. It is also apparent from the testimony that the Food and Drug Administration had ample evidence regarding safety and efficacy to support its action of licensing this drug.

No insurmountable problem exists with the way in which the Company presented product information to the practicing physician except as a matter of semantics—of subtle differences of opinion on the interpretation of words, judgments, and impressions during a time when the Food and Drug Administration itself has been groping with the problem of how to regulate the flow of information to the medical profession. Such differences as exist can more appropriately be resolved by conference rather than by public charges or legal threats. It would appear that the interests of physicians and patients would thus be better served.

After reading the statements and discussions of the hearings on this product, I am more regretful that the circumstances have led to a condition where a good Company, a good performance, and a good drug have so lamentably been characterized by headlines suggesting danger and deceit. The events of the past two weeks only reinforce the need to reexamine the structure of the hearings themselves so that the parties concerned can appear at the outset and provide a factual base against which criticisms can be leveled or improvements proposed. Fair balance has become a watchword in the drug field today. The planning and timing of Congressional hearings might well be so devised as to bring more balance in the final impression left with the public at large.

(A subsequent statement and supplemental information submitted by Senator Nelson follows:)

**STATEMENT BY SENATOR GAYLORD NELSON, CHAIRMAN OF THE MONOPOLY  
SUBCOMMITTEE**

The Monopoly Subcommittee of the Senate Small Business Committee to date has held five days of public hearings on indomethacin, which is manufactured and sold under the trade name of Indocin by Merck & Company. Of our witnesses, 3 were independent physicians from the academic field, 3 from the Food and Drug Administration, 6 from (or on behalf of) Merck & Company, and one, a practicing physician who evaluated the drug for Merck.

The testimony highlighted five problems which are very important to the health and welfare of our people. These are: (1) drug evaluation: (2) what is meant or should be meant by "substantial evidence of safety and efficacy;" (3) the use of euphemistic, soft and unclear language in drug warnings; (4) overpromotion

of drugs, and (5) false and misleading advertising. I shall discuss these problems in order.

As I stated in my opening statement on April 23, the FDA does not engage in the clinical testing of drugs. It approves new drugs solely on the basis of information supplied by the pharmaceutical industry. This raises the question of whether it is sound practice for a firm which has a financial interest in marketing a drug, to direct, arrange, and finance its evaluation. It also raises the question of whether it is possible for an evaluator to maintain objectivity when he is dependent on funds from the company.

Is it a good idea for a physician who is testing a drug to send his data to the company for a statistical analysis while at the same time asking for additional financial support?

Is it a good idea to send a rough draft of proposed results to the firm while at the same time asking for additional money?

Wouldn't it be rather difficult to tell a firm that its product is unsatisfactory especially when a grant for your department at your medical school has been suggested? These are actual cases and I am placing into the record several letters which illustrate the points raised here.

(The letters follow :)

STATE UNIVERSITY OF IOWA,  
Iowa City, Iowa. April 18, 1963.

NELSON H. REAVEY CANTWELL, M.D., Ph. D.,  
*Merck Sharp & Dohme Research Laboratories,*  
*West Point, Pa.*

DEAR DR. CANTWELL: I received your letter this morning and want to thank you for suggesting a grant for the rheumatology section at the University of Iowa.

Since you were here, we have started a number of new patients on indomethacin (the LX capsules). At least three of the patients complained of severe epigastric distress within 30 minutes after taking the capsule. Therefore, in the next few subjects we started them out on 1 capsule twice a day increasing 1 capsule daily until they reached the maximum 6 capsules and believe it or not we encountered no distress. This is the method we will follow for the time being, with our fingers crossed.

The fifteen year old patient with generalized psoriasis and psoriatic arthritis returned for a check-up and is under excellent control on a total dose of 150 mg. per day. She goes to school daily and is able to walk much better than she has at any time during the past year. Another woman (age 45) was admitted with generalized psoriasis and psoriatic arthritis. Before she was admitted to the hospital she was started on terrific doses of steroids which did not control either the painful hands or the skin eruption. The dermatologist started her on 42 mg. Triamcinolone and a few days later we began the indomethacin, 2 tablets at first then increasing daily until she reached the maximum of 300 mg. By the time that we reached the maximum dose she had little or no pain in her hands, was able to make a partial fist and began to feel much better. This morning we have her down to 16 mg. Triamcinolone. She is able to be up and about, has no fever, the skin lesion is receding rapidly and she can actually close her fingers and grasp objects. We started another psoriatic arthritic who has been on steroids for over five years to determine whether or not we can reduce the steroid dose.

Under separate cover I am sending you another batch of the monthly Bulletins in case you need some of these. I have had several calls from Iowa physicians asking me about the drug and two of them have sent patients to us so that we could evaluate them and give them indomethacin.

Again I want to thank you for your kindness and will see you in June.

Sincerely yours,

W. D. PAUL, M.D.

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PAUL J. BILKA, M.D.,  
Minneapolis, Minn., May 8, 1963.

NELSON H. REAVEY CANTWELL, M.D.,  
*Merck Sharp & Dohme Laboratories,*  
*West Point, Pa.*

DEAR NELSON: I have decided to make a preliminary analysis of the patients on the Indocin tablets. Since I started the higher dosage schedule, beginning last summer, there are 63 patients who have been treated from up to eight months, and it certainly looks like we are getting a better result using the minimum dosage

of 100 mg a day, with the vast majority getting 150 mg per day as the minimal dosage.

15 patients had no help.

17 patients recorded slight help (that is less than 25%).

20 patients had significant help (25 to 50%).

11 patients report great improvement (over 50%).

I have not yet analyzed all of the laboratory data, so I cannot give an accurate statement as yet, however certain things are apparent and might be of interest at this time:

18 patients reported severe headache; all but six were able to continue the medication at lower dosage levels or by adding Benadryl; 8 patients reported severe gastrointestinal upset.

One patient (Mr. Jensen) had a history of a DU, but the pretest X-ray was negative. During the third month of 200 mg per day, he developed an active DU. He was continued on the medication in the same dosage and X-rays two and four months later show the ulcer healed.

Another patient (Mrs. Rose) with a known active DU was started on Indocin 150 mg per day and was continued on this for two months because of the marked relief she obtained. At this time however, her GI symptoms increased, the X-ray showed the still active DU and the Indocin was stopped.

A third patient (Mr. Rardin) with a known history of a DU and with signs of activity was given a two month trial of Indocin 75 mg per day. His ulcer symptoms also increased on the medication and the X-ray showed an active DU. All of the other patients had negative X-rays.

I will start going over the charts for the detailed analysis of the laboratory data and will let you know of the results. The work with MK715 is too early to make any comments on except that it seems at least as potent as 615 in the two to one dosage ratio.

I am enclosing the laboratory charges for March and April. Again would you have this made out to St. Barnabas Hospital, Arthritis Research.

I shall soon be enlarging the facilities for out-patient care at the Kenny Institute and we will be in a position to utilize extra funds for our project there. If Merck can make an additional contribution of \$3,000 toward this work, it will be useful and appreciated.

Sincerely,

PAUL J. BILKA, M.D.

THE COLUMBUS MEDICAL CENTER,  
Columbus, Ohio, May 11, 1964.

NELSON H. REAVEY CANTWELL, M.D., Ph. D.,  
Merck Sharp & Dohme Research Laboratories,  
Division of Merck & Co., Inc.,  
West Point, Pa.

DEAR NELSON: The enclosed letter is from a very fine patient, a 45 year woman who is a Ph. D. and teaches at Dennison University. She is quite intelligent, immensely cooperative and completely un-neurotic. I thought you would be interested in her very vivid and articulate description of the adverse symptoms which she encountered with Indomethacin.

I would emphasize that these do not alarm me nor indicate any evidence of organic damage but I am afraid they will offer some practical problems in marketing this drug.

Needless to say, I am very grateful for all of your kind efforts in regard to my trip to Japan.

I'll look forward to seeing you on my return. I think we must get together and plan on publishing some of the data which we have collected. Best regards always.

Sincerely,

NORMAN O. ROTHERMICH, M.D.

P.S. I sent a copy of Dr. Shepard's letter to Elmer.

CLEVELAND METROPOLITAN GENERAL HOSPITAL,  
*Cleveland, Ohio, June 27, 1963.*

NELSON H. REAVEY CANTWELL, M.D.,  
*Merck Sharp & Dohme Research Laboratories,*  
*West Point, Pa.*

DEAR DR. CANTWELL: This is in answer to our telephone conversation. As I mentioned to you in my letter of 26 January, we have treated 51 patients with acute rheumatic fever. I have discussed the whole situation with Dr. Mortimer and our plans for analysis are as follows. Dr. Mortimer is presently analyzing the data and in September Dr. Correa, who participated in the study in Chile, will come to the United States to spend six weeks here going over the data and preparing it for publication. It is possible that we will have a rough draft before that time and if we do we will forward it on to you. In addition, Dr. Correa is going to bring with him the serum specimens that we collect once a month from these individuals. In October I am going to Chile to collect further specimens from the study group. The final analysis of the effect of the drug on valvular heart disease will be completed in January. One of the problems that we will face will be adding the final evaluation of the effect of the drug on valvular heart disease to the analysis of the effect of the drug on the acute phase symptoms. It is my feeling that the two should go together since there is no indication that the drug would or should be effective on valvular heart disease and it is not likely that a second publication will be justified. We are in the process of training two technicians to help us complete the laboratory work.

In going over our financial situation, we will require the money remaining in the original proposed budget to complete this work in an adequate fashion.

With best personal regards,

Sincerely yours,

CHARLES H. RAMMELKAMP, M.D.,  
*Professor of Medicine.*

DUKE UNIVERSITY MEDICAL CENTER,  
 DEPARTMENT OF MEDICINE,  
*Durham, N.C., July 9, 1963.*

Dr. NELSON H. REAVEY CANTWELL,  
*Merck Sharp & Dohme Research Laboratories,*  
*West Point, Pa.*

DEAR DR. CANTWELL: I enclose your completed questionnaire with an attached sheet listing a few further observations. We do not plan on making any further formal report of our findings this year. The protocol sheets are available to you at any time, of course. I would emphasize as I did prior to accepting MK615 for use that the data here are in no way to be interpreted as representing a controlled study. Our patients come from distant towns usually and are often under the simultaneous care of a local physician whose prescriptions are seldom known to us. We simply report what we have noted in our particular and transitory clinic setting.

We need a further supply of both 25 mg and 50 mg capsules of MK615, if these are available. I share with you an impression that these are well tolerated.

Sincerely yours,

GRACE P. KERBY, M.D.,  
*Rheumatism Clinic.*

PAUL J. BILKA, M.D.,  
*Minneapolis, Minn., July 9, 1962.*

NELSON H. REAVEY CANTWELL, M.D.,  
*Merck Sharp & Dohme Research Laboratories,*  
*West Point, Pa.*

DEAR DR. CANTWELL: I have made a preliminary analysis of 50 patients with rheumatoid arthritis who have received MK-615 for at least one week. As I am sure it will take some time before I can complete the clinical evaluation forms on each patient, I thought you might be interested in my impression of the drug at this time.

Of the 50 patients 22 recorded no help or else obtained the same degree of help as from the placebo.

Nineteen patients recorded slight help in the range of 10 to 25 percent improvement.

Eight patients reported significant help which I quantitated, at 25 to 50 percent relief of symptoms.

One patient reported great help, that is, more than 50 percent improvement. Eleven patients who were on medication for at least 3 weeks had the laboratory data which you suggested:

There was no evidence of new ulceration or aggravation of previous X-ray findings of the upper G.I. tract.

Urinary tract disturbance was evident in 4 patients: One had a transient 4 plus albuminuria and 3 showed a few casts. One of these patients who is severely hypertensive had a BUN of 36 which fell to 30 two weeks after stopping the MK 615; no prior BUN was recorded.

Some evidence of liver function disturbance appeared in 7 of these 11 patients: The BSP was elevated in 4; the Cephalin floc was 3 or 4 plus in 5 patients; the alktaise was elevated in 4. Unfortunately I did not do base line values in most of these patients, therefore it is impossible to say if these were the result of this medication in as much as most of these patients were on other drugs such as small doses of steroids, gold, chloroquin or were recently on Butazolidin. However, one patient might be worth indicating in detail and I have enclosed this work sheet that was filled out by Dr. Schultz at the University. One other patient had a normal ceph floc before therapy.

The symptomatic disturbances were relatively minor: One patient reported nausea after a single 10 mg dose, repeated on 2 occasions; one patient said her stools were somewhat loose while on the medication for one month; one patient reported mild itching and erythema with 2 trials of the drug (75 mg a day for 3 days and again on 30 mg for one week); three patients were slightly stimulated mentally and even felt a little jittery on the medication.

What this all adds up to is difficult to say. Certainly many of the patients were grateful for the added relief the medication seemed to offer even if it was not in the great degree such as with steroids. The apparent evidence of hepatic change might be a cause of concern. I would appreciate your ideas concerning extending this study or changing the procedure. I am just about out of the medication and will conclude the study if you wish.

I am enclosing some statements from the laboratories where the test procedures were done on these patients. There may still be a few coming in yet so I will send them later.

Sincerely,

PAUL J. BILKA, M.D.

UNIVERSITY OF UTAH, COLLEGE OF MEDICINE,  
DEPARTMENT OF INTERNAL MEDICINE,  
*Salt Lake City, October 15, 1963.*

NELSON H. REAVEY CANTWELL, M.D., Ph. D.,  
*Merck Sharp & Dohme Research Laboratories,*  
*West Point, Pa.*

DEAR NELSON: It was pleasant to meet with you again and learn first hand of the current status of MK615. Your offer of assistance in the statistical analysis of our data is greatly appreciated. The data summary sheets are completed and will be forwarded to you under separate cover, along with detailed information as to the method of acquiring and computing the scores on each patient. The relative weight of each parameter will be described. For your information and use, we are submitting a summary of our experiences with indomethacin in a double blind crossover and long-term evaluation study. All of the patients included in the double blind study fulfilled the following criteria:

1. A diagnosis of either definite or classical rheumatoid arthritis, using the A.R.A. classification.
2. Active disease as evidenced by swelling and tenderness and/or the necessity of corticosteroids to control symptoms.

Most of the patients have had moderate to severe disease with continuous activity for greater than five years. The patients were paired as closely as possible in regard to age, sex, duration of disease, severity of disease and stage and class of disease. One of each pair, chosen at random, was started on indomethacin, with the other member of the pair being started on placebo. This was done in such a way that neither the patient nor anyone involved in the evaluation of the patient's response knew which medication the patient was receiving at any time. All patients were started on a dose of 200 mg. a day in four divided doses. At the end of one month, the parameters for evaluation were measured

again and the other form of the drug given. After one month on placebo and one month on indomethacin, all patients were started on known drug for the long-term evaluation. All of the examinations were repeated at monthly intervals, or as close thereto as possible. With the long-term evaluation, dosage of indomethacin was varied according to the patient's response and/or side effects.

The following parameters of disease activity were evaluated at each visit. The patient's evaluation of the amount of pain he had had in the previous month, graded on a scale of no pain, slight pain, moderate or severe pain. The number of aspirin taken; the duration of morning stiffness; the amount of corticosteroids or other medication. A cuff compression test of hand grip and a ring size of each finger were taken each visit. Swelling and tenderness of the shoulders, elbows, wrists, fingers, toes, ankles, knees and hips were evaluated according to the following scales: swelling was graded 1 for slight synovial thickening; 2 for swelling that changed the contour of the joint; 3 was swelling that obliterated the normal joint contour; 4 was the presence of a demonstrable effusion. Tenderness was graded 1 for the patient says it hurts when pressure is applied; 2, the patient says it hurts and winces; 3, the patient tries to withdraw from the stimulus. It was possible for the same observer to evaluate the patients greater than 90% of the time. Sub-totals of the swelling, the tenderness, the grip strength, the ring size, the duration of morning stiffness, the amount of pain, the number of aspirin and the milligrams of prednisone or equivalent were obtained for each visit. The difference between the individual parameters and its base line was obtained so that a negative score indicated worsening of the arthritis, whereas a positive score indicated improvement. In the parameters of swelling, tenderness and number of aspirin (300 mg. tablets) a change of 1 was reflected as a change of 1 in the score. A change in the amount of prednisone was scored as the number of milligrams times two. The duration of morning stiffness, a change of  $\frac{1}{2}$  hour was scored as a change of 1. The grip strength was scored as the change in total score of both hands divided by 20, or in other words, a change of 20 mm. of mercury was scored as a change of 1. The sub-totals of the changes in each parameter were then totalled to determine a numerical figure for improvement or worsening of the arthritis. By inspection of the changes in the total score of arthritis, we have evaluated the response to indomethacin as good, fair and none. A good response was considered a response of clearly significant improvement, while on indomethacin, with little or no response while on placebo. A grade of fair was given when there was moderate but definite improvement while on indomethacin, again with little or no response to placebo. The grade none represents either worsening of the arthritis while on indomethacin, or no difference between response to placebo and indomethacin.

We had 31 patients who started the double blind study. Of these, 4 were unable to complete the double blind part of the study because of uncontrollable side effects. The side effects requiring cessation of the study were nausea, vomiting and headache in 2 patients; nausea and headache in 1 patient; and dizziness with nausea and headache in 1 patient. Thus, in the short-term double blind experiment, 68% of the patients had a favorable response; 19% had no demonstrable response; and only 13% had side effects requiring stopping the medication.

The long-term evaluation study has now been under way for ten months, with observations on patients ranging from seven months to ten months in length.

Of the 27 patients finishing the double blind part of the study, 2 were withdrawn before long-term evaluation could be done. One of these was for side effects of the drug, specifically nausea and vomiting, and one patient with a history of bronchial asthma expired with an episode of asthma refractory to all treatment. Of the 25 patients left in the study, 15 had a good response; 9 had a fair response; and 1 showed no response. Of this group, 8 patients have had to stop taking 'Indocin' because of side effects that exceeded the benefit they were receiving. These side effects were dizziness in 5 patients; nausea and dizziness in 1 patient; severe refractory ulcer-type symptoms in 1 patient; giddiness and mental fuzziness in another.

In addition to the double blind study, we have used 'Indocin' in 12 additional patients. Two of these patients had progressive systemic sclerosis; 1 has the fibrositis syndrome; and 1 has an unusual form of hereditary degenerative joint disease. The remaining 8 patients have a diagnosis of either definite or classical rheumatoid arthritis, and were started on the known drug because of severity of the disease process. Four of these were hospitalized because of their arthritis at

the time 'Indocin' was started. Of this group, we have had a good response in 9 patients; a fair response in 2; and 1 patient had side effects that required cessation of the drug before any effect could be noted. Of this group, 5 patients have required stopping 'Indocin' because of side effects, even though the response had been fair or good.

In our work with 'Indocin', we have found that headache, while not an infrequent side effect, has not been particularly difficult to control, responding either to antihistamines or to reduction in dosage of 'Indocin'. The dizziness, nausea and vomiting, however, have been refractory to most efforts at control with the exception of stopping 'Indocin'. Using antacids, anti-emetics, etc. has had no effect in stopping this complication. We have found in a few patients that stopping the drug for a period of time, and then re-starting it, has been successful. We have made frequent checks of blood chemistry and hematological studies, and have found no disturbance with hematopoiesis or hepatic or renal toxicity. We have had several patients on 'Indocin' develop peptic ulcer disease, and have had two episodes of massive upper G.I. bleeding. However, in the 2 patients with upper G.I. bleeding, 'Indocin' has been continued after their acute episode and these patients are now 9 months and 4 months post-hemorrhage with no symptoms, or only minimal symptoms remaining. All of the patients who have developed ulcers have also been on corticosteroids.

The possibility of obtaining fewer side effects with as good or better results from the use of the capsule form of 'Indocin' has been of interest to us. As we discussed with you, we would be anxious to try the capsules also in a double blind crossover fashion, similar to our study with the tablet form. To run such a study with the number of patients we would have available would require 90 bottles of 25 mg. 'Indocin' capsules, and 90 bottles of placebo capsules. Anticipating the number of patients who will respond favorably to this, and in whom we would like to continue the capsules past the double blind study, we would need approximately 400 bottles of 25 mg. capsules to carry these patients for a total of six months. We feel that there would be certain other studies that should be pursued in the use of 'Indocin'. These would include correlation of blood level with therapeutic effect and with side effects or toxicity. Because of the peculiar mental reactions we have had, we would feel that an attempt to correlate electroencephalographic findings with blood level and with effect should be done. We would like to receive some of the bulk 'Indocin' so that its effect in experimental models of arthritis could be pursued shortly. Ultimately, the determination of Indocin's place in the therapeutic armamentarium of the rheumatologist should be done. Several of these things will require more detailed planning before they can be accomplished. However, the capsule double blind study and use of the bulk drug in experimental models of arthritis could be accomplished as soon as we can receive the necessary drug.

From our experience with your drug 'Indocin', we feel that you have developed an agent that has a definite place in the treatment of rheumatoid arthritis, even though we have had considerable disappointment in the amount of side effects. We would feel that with further work, maybe the difficulties might reasonably be expected to be overcome. Although it is still too early to tell, we have noticed in 4 or 5 patients, a tendency for the development of remission of their disease activity. Whether they are truly going into remission remains to be seen, but the evidence suggesting that they are is there.

We can discuss the necessary financial support for a double blind study using capsules when the decision is reached to initiate the study.

Very truly yours,

JOHN R. WARD, M.D.

STANFORD UNIVERSITY SCHOOL OF MEDICINE,  
STANFORD MEDICAL CENTER,  
DEPARTMENT OF MEDICINE,  
*Palo Alto, Calif., August 22, 1963.*

NELSEN H. REAVEY CANTWELL, M.D.,  
*Merck Sharp & Dohme Research Laboratories, West Point, Pa.*

DEAR DR. CANTWELL: I am sorry I haven't answered your previous request for information about Indomethacin. For various reasons I have not put our results together yet but will do so in the not too distant future. This was our first effort at drug evaluation, and I am afraid we have been somewhat inefficient in maintaining precise up-to-date evaluations of the patients. Though all the necessary information is in their charts, we have not extracted it all as yet.

Our impression of the drug remains good. It is clearly not the answer to rheumatoid arthritis and has not been helpful in those few instances of connective tissue disease where we have tried it; but in a significant number of patients it is of decisive benefit when other medications have failed.

I am writing to you about a financial question. We have obtained a modest amount of laboratory information on our patients which the patients were guaranteed would not be charged to them. The day of reckoning is approaching with the hospital when they insist that I settle accounts. I am therefore writing to ask what mechanism you would propose that we employ to obtain the money from you to meet these expenses?

Many thanks for your consideration.

Sincerely,

HALSTED R. HOLMAN, M.D.

SCRIPPS CLINIC AND RESEARCH FOUNDATION,  
*La Jolla, Calif., April 29, 1963.*

ELMER ALPERT, M.D.,

*Merck Sharp & Dohme Research Laboratories, West Point, Pa.*

DEAR DR. ALPERT: I thought I would drop you a little progress note as to what we are doing with the MK-615 that you sent to us, and at the same time, ask if you could send me some more.

With the full realization that our clinic material is too limited in numbers for a large double blind study, we have been merely using MK-615 in the management of some of our patients and recording our impressions of it. Today I can merely tell you that we have seen no untoward effects from it although our top dose has been only 250 mgs as per your suggestion. We have also found that patients tolerate MK-615 together with ASA dose of 4 grams a day without signs of salicylate intoxication. I can also say that the persons on MK-615 seem to be doing quite well although it does not seem to be holding one 40 year old lady.

Finally, regarding our equilibrium dialysis study with MK-615 we have found that MK-615 does, indeed, bind to the same site on albumin that is bound by the  $I^{131}$  labeled Uroko. As you recall, sodium salicylate also binds to this site but we think that MK-615 has a stronger bond than does sodium salicylate.

Meantime, with your generosity I would greatly appreciate some more 50 mg MK-615 tablets so that we may continue our few patients on it.

Very sincerely yours,

RICHARD S. FARE, M.D.,  
*Head, Division of Allergy and Immunology.*

NEW BEDFORD, MASS.,  
*February 18, 1964.*

NELSON H. R. CANTWELL, Ph. D., M.D.

*Merck Sharp & Dohme Research Laboratories,  
West Point, Pa.*

DEAR NELSON: I am sending to you the initial MK-615 Clinical Evaluations as I originally submitted them. Under comments, where previously no comments had been made on any of the forms, I have brought my data up to date to the time when each patient discontinued the medication.

As you may see from these comments, I failed to note any beneficial effect on either a decrease in steroid dosage or any relief which may have been obtained from these patients who all were suffering from some allergic disorder.

My initial impression after evaluating the original data therefor held it does not seem to be of any benefit in allergic diseases. I might note that I have had four allergic patients with bursitis in whom I took the liberty of trying this drug and had beneficial result in all four. I was patiently waiting the recurrence of my own gout to see if it would be of benefit but fortunately or unfortunately depending upon your point of view, I myself have not had the chance to evaluate it personally.

Because of the poor data I did obtain, I saw no reason to go ahead and use the capsule form of M-615 and have not done so. If you feel there is a dramatic difference in the therapeutic benefit, which I would doubt, I could try a group of selected patients on this if you so desire.

Edward Joyce was in to see me and informed me that you are considering a topical preparation of this which may help in dermatological disorders. I indicated

to him that I would be willing to carry out a clinical trial if you felt this was promising.

As far as compensation for the work done, I feel a grant of \$1500.00 would be fair if you so see fit.

I am sorry you have been too busy to come in to this area. I will be at the American College of Allergy meeting in Miami the first of March. If you have that in your plans I will be happy to see you then. Best regards from Elaine. Hope all is well with you.

Very truly yours,

PAUL CHERVINSKY, M.D.

MINNEAPOLIS, MINN.,  
June 24, 1963.

NELSON R. CANTWELL, M.D.,  
*Merck Sharp & Dohme Laboratories,*  
*West Point, Pa.*

DEAR NELSON: I have gone over the data on the 63 patients I reported to you earlier this month and have extracted the information you recently asked about.

1. 40 patients have been on 150 mg or less of Indocin per day. 20 of these reported no or slight help and 20 reported significant (25% to 50%) or great (more than 50%) help.

2. 15 patients had 200 mg per day and 7 reported no or slight help and 8 reported significant to great help.

3. 8 patients had more than 200 mg per day. 5 reported no or slight help and 3 reported significant or great help.

4. All patients had rheumatoid arthritis.

5. There was a definite increase in GI symptoms and especially headache with increase in dosage. There was very little headache on 100 mg or less per day. Gastric irritation seems to be an increasing problem.

6. I have had little experience with non-rheumatoids so far, but 1 patient with Reiter's disease had an excellent response: 1 patient with chronic gout had a good response and 1 patient with Scleroderma had slight help.

7. Regarding headache and migraine; the very day you called, the first patient I asked the question of stated that she had been a frequent sufferer of migraine before developing her arthritis. She had been free of headache until it recurred with Indocin. However, she stated this headache was different from what she remembered her migraine was like. I haven't had the opportunity to put the question to all patients, but several have denied previous migraine, yet 3 have admitted to prior migraine.

8. 39 of the 63 patients have been on Indocin for 2 months or more, some over 8 months. It is my plan to carry as many on long-term therapy as tolerate and benefit from the drug. New patients are being constantly added as I presume is your desire.

Sincerely,

PAUL J. BILKA, M.D.

PAUL J. BILKA, M.D.,  
Minneapolis, Minn., August 29, 1962.

NELSON H. REAVEY CANTWELL, M.D.,  
*Merck Sharp & Dohme Research Laboratories,*  
*West Point, Pa.*

DEAR DR. CANTWELL: During the last month I have been carrying on a new trial with MK-615 using the higher dosage range which you suggested. A preliminary analysis of 22 patients indicates rather significant improvement in the results using this higher dosage. All patients have rheumatoid arthritis, and the majority have been on the lower dosage trial. The results after 2 to 4 weeks therapy are as follows:

Four patients report no significant improvement.

Five patients report 10 to 25 percent subjective improvement.

Twelve patients report 25 to 50 percent improvement.

One patient reports marked, or over 50 percent improvement.

There have been 2 complaints of nausea caused by the higher dosage and one patient who had a previous active duodenal ulcer, and also is on 0.6mg beta dexamethasone per day developed an active DU on 100mg MK-615 per day. One other patient complained of headaches. I have not, as yet, analysed the laboratory data, but will do this shortly when I fill out the regular investigative forms. I thought, however, that you would be interested in these preliminary findings.

Sincerely,

PAUL J. BILKA, M.D.

DUKE UNIVERSITY MEDICAL CENTER,  
DEPARTMENT OF MEDICINE,  
*Durham, N.C., December 10, 1963.*

Dr. NELSON H. REAVEY CANTWELL,  
*Merck Sharp & Dohme,*  
*West Point, Pa.*

DEAR DR. CANTWELL: Enclosed are the original data sheets for patients who received Indocin tablets. You will note that some are continuing on capsules. Another 24 patients started on capsules since August 1963, and these data sheets are retained here at present. The presently enclosed sheets represent for the most part those patients covered in the June 1963 summary which I sent to you.

Sincerely yours,

GRACE P. KERBY, M.D.,  
*Rheumatism Clinic.*

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DUKE UNIVERSITY MEDICAL CENTER,  
DEPARTMENT OF MEDICINE,  
*Durham, N.C., December 8, 1963.*

Dr. NELSON H. REAVEY CANTWELL,  
*Merck Sharp & Dohme Research Laboratories,*  
*West Point, Pa.*

DEAR DR. CANTWELL: I am sorry to have missed seeing you at the recent Boston meeting. However I do want to mention two patients in regard to Indocin, one for your own information and one to raise a question re contraindication to use of Indocin.

A 19 year old CF with unequivocal SLE manifesting most strikingly as acute nephritis with good renal function was admitted in October while I was out of town. Because she was not sufficiently critically ill to require immediate ACTH or steroids, my colleagues started her on Indocin, 50 mg per day increasing over about one week to 150 mg per day, at which time I first saw her on return to town. An originally normal BUN rose slightly in the first few days and then to 47 mg% by the time I first saw her. On the chance that this was the phenomenon you have noted with Indocin in the presence of pre-existing renal disease, Indocin was discontinued. The BUN returned to normal over the next few days.

A young WM with chronic rheumatoid arthritis, on phenylbutazone, was admitted recently to the V.A. hospital here with GI symptoms. Two gastric ulcers near the cardia were demonstrated. He was to be discharged this past weekend with ulcers healing well and promptly, to come to the Rheumatism Clinic at Duke for the first time either this Thursday Nov. 12 or Nov. 19, referred specifically for Indocin. However, recalling the report at the June meeting of patients with previous peptic ulcer/developing multiple gastric ulcers, I question whether Indocin may not be contraindicated in this patient. If it is at all possible to have your comments on any further information concerning the GI tract during Indocin therapy prior to this patient's scheduled first visit to the clinic, I shall most appreciate having them. He has to travel 150 miles from his home, doing his own driving despite severe rheumatoid arthritis. Had I realized that I would be unable to get your comments in Boston, I would not have suggested such an early appointment for the patient.

Following our recent telephone conversation, I sought and obtained permission from NIH to use up to \$3600 from my research grant for the proposed work with Dr. Luscher. I am therefore proceeding with my plans as related earlier. I also contacted Dr. Stead, to ask if funds of the sort you proposed were permitted by the department. He was entirely agreeable and felt that such uncommitted funds offered greater latitude in opportunity to work and visit in other laboratories, as well as provide enjoyable contact with the commercial firm. From my own point of view the added advantage of being able to conserve my NIH funds in greater part for the operations in my own laboratory which would continue on a limited scale in my absence. Therefore I am free to accept any research funds from Merck, if you still feel as before that the type of informal report sent you last June on our experiences with Indocin constitutes a valid basis for such funds. This type of informal report on our experience can continue to be furnished, although as I recounted earlier, formal reports from here will never be proper due to the long distances our patients travel, making closer supervision impossible. In answer to your inquiry as to institutional and departmental requirements in addressing funds, the funds from Sandoz three years ago were addressed as follows, and this would be the preferred method now:

Name of Payee: Anna H. Hanes Research Fund, Department of Medicine,  
payable to Dr. Grace P. Kerby.

Street Address: Duke University School of Medicine.

City: Durham, N.C., 27706.

Sincerely yours,

GRACE P. KERBY, M.D.

UNIVERSITY OF OREGON MEDICAL SCHOOL,  
DEPARTMENT OF PHARMACOLOGY,  
Portland, Oreg., February 25, 1964.

Dr. NELSON H. REAVEY CANTWELL,  
*Merck Sharp & Dohme Research Laboratories,*  
*West Point, Pa.*

DEAR DR. CANTWELL: Herewith are the special case reports for 11 cases who have had trial of the "Indocin" capsules. The number of the cases are from 3518 to 3528. For the record, I am retaining the additional case record forms that you sent and numbered from 3529 to 3567. These unused forms will be used for any additional cases that are placed on "Indocin" capsules. However, if you wish these blank case forms returned, I can do that.

As you know, I sent you a copy of the individual case records for all the patients (21 cases) who have received both the tablets and the capsules of "Indocin". I am currently writing this up as a short report for possible publication as a research note in CURRENT THERAPEUTIC RESEARCH. When I complete this short note, I shall forward you a copy for your inspection.

I hope that your case reports for the capsules are coming in satisfactorily and you can get off the material to the FDA. Good Luck!

With best wishes,

NORMAN A. DAVID, M.D.  
*Professor of Pharmacology.*

#### STATEMENT OF SENATOR NELSON—Resumed

One of our witnesses, Dr. Donald Mainland, a medical doctor and one of the most famous biostatisticians in this country, has recommended that the evaluation of drugs be taken entirely out of the hands of the pharmaceutical industry, an idea which merits study. Even if the drug firms continue to do animal, and to some extent clinical studies, approval for marketing by the FDA should be based, at the very least, on studies under its direction. Perhaps it may be a good idea to establish a national drug institute, the purpose of which would be to evaluate drugs, in-house and/or by contract. In other words, it seems reasonable that there should be an independent, careful and scientific evaluation of a drug to secure FDA's approval. We are studying this problem and may be prepared to propose legislation in this field sometime soon.

The second problem is FDA's requirements for evidence of safety and efficacy. The statute requires "substantial evidence" of safety and efficacy which means "evidence consisting of adequate and well-controlled investigations." On December 7, 1964, the medical officer in charge of the New Drug Application for Indocin stated in her summary that "There is a paucity of controlled studies in this massive NDA." On March 15, 1967, Dr. David Hurwitz, M.D. of the FDA's Bureau of Medicine in referring to claims of efficacy in osteoarthritis of the joints, other than the hips and muscular skeletal disorders, found that "136 out of 137 studies are deficient in technique and incapable of standing up to critical examination; it is unfortunate that the company and its investigators do not use the more sophisticated investigative techniques that have been evolved to evaluate new drugs."

Dr. Hurwitz also stated that:

"In view of the wide-spread acceptance of Indocin and its seeming benefit in Rheumatoid Arthritis, it is an unwarranted conclusion to say at this time that the drug is of no usefulness in this disease. However, since these excellent studies by Cooperating Clinics Committee and by Donnelly et al. in the British Medical Journal cast considerable doubt on the efficacy of Indocin, further studies of equal or better quality and of longer duration are in order to determine the place of this drug in the physician's Armamentarium. This re-evaluation is particularly necessary given the toxicity of Indocin which renders the drug totally unfit for use if a significant therapeutic benefit cannot be established."

The question then arises whether a "significant" therapeutic benefit has been

established for rheumatoid arthritis, which presents the largest potential market for indomethacin, Indocin).

Perhaps an answer can be found in Dr. Hurwitz's memorandum of August 25, 1967, in which he stated that: "At the present time, then, it would seem wise to consider Indocin as probably effective in rheumatoid arthritis pending further studies in this area." The word "probably" should be emphasized.

How can we reconcile the FDA medical officers' opinion that there is a "paucity of controlled studies" and that the drug is "probably effective" with the statutory requirement of substantial evidence of efficacy?

How can we reconcile the requirement of "substantial evidence" of safety with the opinion of an FDA medical officer that " \* \* \* Indocin has shown a similar propensity to cause a wide variety of serious and sometimes fatal reactions, and its clinical usefulness has been limited by its toxicity."

The American Medical Association's New Drugs, 1967 edition, states that:

"Central nervous system effects (headaches, usually severe in the morning; vertigo; light headedness; mental confusion) occur during the early weeks of therapy in about 20% to 30% of patients taking indomethacin. Drowsiness, convulsions, depression and psychic disturbances such as depersonalization have also been reported. \* \* \* Indomethacin should be regarded as being potentially ulcerogenic. It may produce single (or) multiple ulceration of the esophagus, stomach duodenum or small intestine. Cases of perforation and hemorrhage, a few of them fatal, have been reported."

I am inserting at this point a summary of side effects reported by Merck's investigators.

(The summary follows :)

#### SIDE EFFECTS—INDOCIN

"The patient complains of a distressing lightheadness, a feeling of being in outer space, a feeling of the head being foggy and a feeling of difficulty in concentration or in cerebration. There may or may not be an associated violent headache and in a few cases, the headache was so violent that it was predominant or alone. In a few instances, these symptoms have been so severe as to be totally incapacitating and even prostrating" (Oct. 9, 1962).

Dr. NORMAN O. ROTHERMICH,

*Columbus Medical Center, Research Foundation, Inc., Columbus, Ohio.*

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"The greatest deterrent to increasing dosage to an effective level is the appearance of cerebral toxicity. This manifests itself clinically in excruciatingly severe headaches, dizziness, lightheadedness, disturbances of sensorium, a feeling that the head is floating away or even separating from the body and feelings of detachment from reality" (June 12, 1963).

Dr. NORMAN O. ROTHERMICH.

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"As higher dosage levels are approached, it is to be expected that the incidents of cerebral toxicity goes up proportionately and this, in my opinion, represents a not insignificant disadvantage to the drug for it reduces the number of arthritics who can be benefited by the drug. . . . on the other hand some patients have developed disabling cerebral toxicity . . . on comparatively low dosages" (Oct. 12, 1963).

Dr. NORMAN O. ROTHERMICH.

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"I am sorry to report but I am sure you should know, that we saw rather severe dermatitis in one patient after taking four tablets (100 mg) of MK-615 over a 24 hour period. We sincerely hope we will have better results to report in the future" (Apr. 24, 1962).

Dr. H. M. MARGOLIS,

*Pittsburgh, Pa.*

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"We had 31 patients who started the (short term) double-blind study. . . . 13% had side effects requiring stopping medication." "In our work with Indocin we have found that headache while not an infrequent side effect, has not been particularly difficult to control, responding either to antihistamines or to reduc-

tion in dosage of Indocin." "We have had several patients on Indocin develop peptic ulcer disease, and have had two episodes of massive upper GI bleeding." "We feel that there would be certain other studies that should be pursued in the use of Indocin. These would include correlation of blood level with therapeutic effect and with side effects or toxicity. Because of the peculiar mental reactions we have had, we would feel that an attempt to correlate electro-encephalographic findings with blood level and with effect should be done." "We have had considerable disappointment in the amount of side effects" (Oct. 15, 1963).

Dr. JOHN R. WARD,  
*College of Medicine, University of Utah, Salt Lake City, Utah.*

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"I would be very anxious to receive further information from you concerning other clinical experiences with Indocin. Our experience to date with the material you supplied us has been limited because of the significant incidence of headaches and gastrointestinal complaints. This has made me reluctant to use it in a number of instances where I might wish to have done so. I would therefore greatly appreciate any further data you have relating to this drug that might influence our use of it" (Jan. 9, 1968).

Dr. KURT J. ISSELBACKER,  
*Harvard Medical School,  
Massachusetts General Hospital, Boston, Mass.*

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"Toxic Manifestations: Only 6 of the 27 failed to show some evidence of toxicity, but in 2 others showing GI toxicity and 1 with rash the medication was discontinued. Only 1 of the 6 males showing 'excellent' therapeutic response showed clinical toxicity—GI pain" (Jan. 2, 1964).

Dr. WM. C. KUZELL,  
*San Francisco, Calif.*

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"I believe you have an excellent skeletal analgesic but I am worried about the headache, nausea and emesis and mental confusion" (Mar. 20, 1963).

Dr. HAROLD M. ROBINS,  
*Delaware Avenue Medical Center, Buffalo, N.Y.*

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"In brief, the acute data indicate that indomethacin is approximately as effective as aspirin in the control of fever, joints and other acute manifestations" (Sept. 4, 1963).

Dr. EDWARD A. MORTIMER, JR.,  
*Cleveland Metropolitan General Hospital, Cleveland, Ohio.*

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"Dr. Gum continues to find that Indocin is an interesting and effective agent in rheumatoid arthritis. The incidence of headaches, however, is between 85% and 100%. This is causing him real concern. He commented that this would also seriously impair any presentation to FDA. \* \* \* Dr. Burch . . . refuses to do further clinical investigations and is not too happy that any of his staff continues to do them" (May 6, 1963).

Memo R. R. Robert to Dr. N. H. R. Cantwell on "Progress of Study of Indocin" Merck Co.

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"The side effects occur in about ten percent of the patients and in nearly one-half of this group, the drug had to be discontinued. The side effects are nausea, headaches and lightheadedness" (Oct. 3, 1963).

Dr. W. D. PAUL,  
*University Hospitals, University of Iowa, Iowa City, Iowa.*

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"We also discussed with Dick Rebert we definitely feel that you should set up a double blind on the drug. . . ." "It is with some disappointment that we are reaching the conclusion that the effect of the drug is largely subjective and

would most clearly be assigned to the category of analgesics rather than anti-phlogistic agents according to our present experience" (Oct. 1, 1963).

DR. R. W. PAYNE,  
*McBride Clinic, Inc., Oklahoma City, Okla.*

"In the fall of 1962, I submitted data on the tablet form of Indocin on the government forms. I have no additional data. My results were generally unsatisfactory and so I discontinued use of the drug" (Jan. 7, 1964).

DR. JOSEPH E. GIANSIRACUSA,  
*San Jose, Calif.*

"I don't believe I will continue to use Indomethacin until some other reports are available from people in this country . . . the only possible use that I think we might make of it sometime would be in the treatment of acute gout. . . . I think a study of Indomethacin compared with Placebo might be something the house officers might like to undertake sometime in the future. . . . We have no plans at this time" (Jan. 9, 1964).

DR. J. W. HOLLINGSWORTH,  
*School of Medicine, Yale University, New Haven, Conn.*

"I have learned that two other patients on Indocin have developed peptic ulcers, one with perforation necessitating operation. This now, in our series of approximately 100 patients, makes at least six, and perhaps seven, ulcers. Certainly this agent is ulcerogenic to a degree that will make it difficult to continue to advise its use" (July 9, 1963).

DR. CARL M. PEARSON,  
*School of Medicine, University of California Medical Center, Los Angeles, Calif.*

"My incidence of headaches in this group has been about 33%. I have discontinued the drug as soon as headaches occur because I have not known how to evaluate this from a toxic point of view. Until we know more about its causes, I don't think we should continue it in the presence of headaches" (June 21, 1963).

DR. EDWARD E. ROSENBAUM,  
*Portland, Oreg.*

"However, the incidence of side effects that we have more recently encountered seems to us to be at the present time too great to have this medication used as therapy in general office practice" (June 11, 1963).

DR. CARL M. PEARSON.

#### STATEMENT OF SENATOR NELSON—RESUMED

In the December 17, 1965 issue of Medical World News, Dr. Charley J. Smyth is reported to have claimed that indomethacin is the most promising antirheumatic agent since cortisone. Yet, less than two years later in an article in the April 1967 issue of Consultant with the title, "Treating Rheumatoid Arthritis: What's Most Apt to Succeed?" Dr. Smyth mentions indomethacin only in passing. Steroids, phenylbutazone, antimalarials, gold treatment and surgery are discussed, but not indomethacin. Dr. Smyth's explanation to the Subcommittee is that space was limited. Would it not be reasonable to assume that if space is limited, the most important items would have been included and the marginal ones left out?

Doctors Calabro and Smyth presented their personal views of the drug on behalf of the manufacturer. The only independent doctor who had the opportunity of inspecting the NDA file was Dr. O'Brien of the University of Virginia Medical School. His judgment was that although there was considerable testimonial evidence, there was relatively little scientific evidence. Dr. L. A. Healy in the article which Senator Scott has kindly put into the record, stated that:

"In a chronic disease such as rheumatoid arthritis, which is marked by spontaneous remissions and exacerbations, where both the patients and physicians naturally are hoping for improvement, the subjective impression of the efficacy

of any drug is inadequate to judge its value. It is apparent that more reliable information on effectiveness of indomethacin can be obtained from the third group, the controlled studies."

Four independent, well-controlled studies have shown that indomethacin is not more effective in rheumatoid arthritis than is aspirin, which is still the drug of choice according to the AMA.

The third problem is the use of euphemistic language in warnings and contraindications when strong language is required. The reviewing medical officer recommended that the following wording be included as a contraindication: "Indocin should not be administered to children."

This is clear and strong, but this essential warning ended up as follows:

"Since the experience with Indocin in children is limited, it is recommended that this drug should not be administered to pediatric age groups until the indications for use and dosage have been established."

There is quite a difference in clarity and conciseness between the version recommended by FDA's medical officer and the one adopted by the firm and finally approved by the FDA. The result was that the message did not get through. In a poll by Modern Medicine which was reported in its August 1, 1966 issue, almost 10% of the pediatricians who reported treatment of rheumatoid arthritis prescribed indomethacin during a thirty day period in the first year of its marketing life. During this time (first year of its marketing life by July 1966), five deaths in children being given this drug were reported. Up to the beginning of 1968, 9 deaths in children were reported. A stronger warning was adopted later at the insistence of the FDA.

Why didn't the FDA insist on a strong warning in the first place? The reason given by Dr. Hodges was that there wasn't enough data to show that it was dangerous or safe for children. Yet, even though the statute insists that substantial evidence of safety and efficacy should be presented for uses of a drug, it appears that the FDA modified the requirements and used soft warnings for children because the drug was tested in only 55 children and there was not enough evidence to show lack of safety and efficacy.

The fourth problem is that of the overpromotion of Indocin. Here is a drug with very limited uses and yet, it is reported that it has a wholesale sales volume of over \$40 million per year and is one of the 200 most frequently prescribed drugs.

The New Drug Application for Indocin was originally approved for use in only the following 4 conditions:

- (a) Rheumatoid arthritis.
- (b) Rheumatoid (ankylosing) spondylitis.
- (c) Degenerative joint disease (osteoarthritis) of the hip.
- (d) Gout.

The most frequently occurring illness is Rheumatoid Arthritis, for which, according to AMA's NEW DRUGS, aspirin is the drug of choice, and Indocin should be used only when aspirin fails or cannot be used.

The FDA testified that Indocin is being used beyond its approved indications and that some physicians regard the drug as a general purpose analgesic, antipyretic, anti-inflammatory agent and the 1966 promotion of the drug featured this effect.

The fifth problem is that of false and misleading claims which, the FDA testified, have been made for this drug and which necessitated a remedial "Dear Doctor" letter and a Bureau of Medicine recommendation of prosecution under the Food and Drug Act.

I am also inserting at this point a staff memorandum dealing with Merck's advertisement of Indocin in the British Medical Journal of 1967-68.

(The memorandum follows:)

#### MEMORANDUM

To : Senator Gaylord Nelson, chairman, Monopoly Subcommittee

From : Benjamin Gordon, staff economist

Subject : Comparison of ads for Indocin in the British Medical Journal and the Journal of the American Medical Association, 1967-68

None of the advertisements for Indocin in the British Medical Journal (BMJ) in the years 1967-68 included any prescribing information. Some of these ads say, "Detailed information is available to physicians on request." Others do not even make this reference to indicate the desirability of obtaining information on the drug prior to prescription and administration.

The ads quote from papers favorable to Indocin. But, they do not, at any time, mention warnings, precautions, contraindications, or side effects. Not one of these ads refers to deaths of children from Indocin—a subject which is required to be mentioned in all ads run in the U.S. None of the ads warns against use of the drug in pregnant women or people suffering from peptic ulcer.

The fact that Indocin may cause reactions of the central nervous system, gastrointestinal reactions, skin reactions, blood disorders or eye-ear problems as reported by Merck's clinical investigators, is not even mentioned. But, because of FDA regulations with respect to advertising, all U.S. ads do carry these warnings.

Furthermore, almost every ad which has appeared in the BMJ in the last 18 months has promoted Indocin for bursitis and other muscular problems for which the FDA has not approved claims in this country. Thus, although Merck is not allowed to promote Indocin for these conditions in the U.S., the firm is actively promoting it for them abroad. If the scientific, clinical evidence of the value of Indocin in the treatment of bursitis is not sufficient to recommend it for consumption by Americans for this purpose, is there any reason to believe that it would benefit the British people?

Thus, by praising Indocin, and pointing to its benefits, but by failing to call attention to the drug's negative aspects, Merck is presenting an unbalanced picture to the British Medical profession.

#### STATEMENT OF SENATOR NELSON—RESUMED

In summary, FDA's criticism of Merck with respect to Indocin is as follows:

1. Merck made a promotional letter out of a remedial letter to doctors. An additional letter had to be sent out at the insistence of the FDA to correct the first one.

2. Merck used an older article as a testimonial when a more recent but less favorable article was available well before the ad was created and published. In addition, the second article favored a competitive product to a great extent: 15 patients preferred phenylbutazone: 10 found them equally effective; and one preferred indomethacin.

3. Claims of effectiveness were based on dosages far in excess of the upper approved safe limit when the drug was marketed in this country in capsule form.

4. Promotion over the first year of its approved marketing improperly presented the drug to the medical profession—both as to the range of its effectiveness and margin of safety.

The testimonial letters submitted by Merck & Company for the hearings record reflect in general a lack of enthusiasm for the potentialities and safety of Indocin and appear to confirm the testimony of the Food and Drug Administration, with respect to the limitations of Indocin and the unwarranted claims made for it in its advertising and promotion.

Some significant statements from Merck's submissions follow:

Dr. Kemper: Drug of choice rheumatoid spondylitis and degenerative arthritis. Not nearly as effective in peripheral rheumatoid arthritis as in others.

Dr. Hamaty: "Regarding the double blind method in evaluating drugs for rheumatoid arthritis . . . it is the best we have available at this time."

Dr. Duncan S. Owen, Jr.: "Indocin is no panacea in the treatment of rheumatoid arthritis but it definitely has a place in its treatment. \* \* \*"

And what is the place?

Dr. Owen says that aspirin should be given first "in essentially all cases of rheumatoid arthritis. If after several weeks no clinical improvement is experienced, another agent should be added. We frequently use Indocin as the second agent and will continue to use it in this capacity. Also, we have found the drug to be helpful in selected cases of osteoarthritis, acute gouty arthritis, and ankylosing spondylitis."

Dr. Donald F. Hill: " \* \* \* our group did conduct a clinical trial to study efficacy and toxicity before Indocin was marketed. These studies were limited primarily to rheumatoid arthritis and, unfortunately, did not show consistent results. There were a few patients who felt that Indocin gave them much more relief than other analgesics or anti-inflammatory compound, but we did not feel that the drug altered the course of the disease. We continue to use Indocin in a limited number of patients where they feel it has been of help to them. Unfortunately, a number of our patients were unable to tolerate the drug."

Dr. Arthur Dobkin: "I have found 'Indocin' to be beneficial in a selected and limited number of arthritis patients."

Dr. Jack Zuckner: "If there is a doubt about Indocin in the treatment of rheumatoid arthritis, I believe that double blind studies should give the most reliable information in its efficacy."

Dr. E. G. L. Bywaters: "I feel that this drug is useful in certain patients with rheumatoid arthritis and has about the same potency as aspirin. It is, however, more expensive and we therefore tend to use it when patients cannot tolerate aspirin and sometimes to wean them off steroid medication. . . . It seems useful also in ankylosing spondylitis and we have used it there in such cases who have developed intolerance to phenylbutazone. \* \* \*"

Dr. Harry F. Klinefelter: "\* \* \* I have found Indocin very helpful in a limited number of arthritics who have not responded to other medication, such as aspirin. Butazolidin and Tachearil. There are a small number of people with rheumatoid arthritis who do extremely well on Indocin, and if they respond, they respond to doses of 75 mg. a day or less."

In addition, Mr. Gadsden, during the course of his testimony, made the following statement:

"I would furthermore like to call your attention to a quotation of 1967 from the recognized publication, NEW DRUGS, as published by the AMA. It says that because 'Indocin' has produced relief in acute attacks within 48 hours, and because it lacks untoward effects of Colchicine, some physicians consider it to be the drug of choice for these attacks."

The complete paragraph from the AMA 1967 publication from which the excerpt was taken and which presents a more limited picture of the drug's uses is as follows:

"Indomethacin produces anti-inflammatory effects in patients with gout and may be as effective as phenylbutazone in its promptness of action and the degree of relief it provides. Because it has produced relief in acute attacks within 48 hours, and because it lacks the untoward effects of colchicine, some clinicians consider it to be the drug of choice for these attacks; however, controlled trials are needed to determine how its effectiveness compares with that of colchicine. Indomethacin may be useful as a supplement to colchicine in the management of severe cases of gout. Whether it is useful as a prophylactic agent in gouty arthritis remains to be established."

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[From the Medical Letter, vol. 10, No. 10, May 17, 1968]

#### INDOMETHACIN (INDOCIN)

Indomethacin (Indocin-Merck) is widely used as an anti-inflammatory analgesic drug in the treatment of rheumatoid arthritis and spondylitis, osteoarthritis, and gout (Medical Letter, Vol. 7, p. 89, 1965). Enthusiastic reports of its effectiveness followed the introduction of the drug in 1965, but many of the reports published since that time have been much less enthusiastic, some even questioning whether the drug was more effective than placebo.

In the mass of conflicting studies of indomethacin, not many have been controlled and very few of the controlled studies have been so designed as to give clear answers about the usefulness of the drug. Frequently other drugs were used simultaneously and doses varied widely. The numerous uncontrolled studies have generally ignored the variable course of rheumatic disorders and the effectiveness of placebos in many patients. On the basis of both published reports and their own experience, Medical Letter consultants believe that indomethacin is a useful drug, but that its usefulness is limited by its frequent and sometimes severe side effects.

*Rheumatoid arthritis.*—Indomethacin appears to have about the same anti-inflammatory and analgesic effectiveness as aspirin in patients with rheumatoid arthritis (R. S. Pinals and S. Frank, New Eng. J. Med., 276:512, 1967). Aspirin is better tolerated by most patients and it remains the drug of first choice for rheumatoid arthritis. Indomethacin is not as hazardous as the corticosteroids, gold, or phenylbutazone (Butazolidin), however, and it is worth a trial in patients who cannot tolerate aspirin. Some investigators have observed additive effects when indomethacin was given along with aspirin; other investigators have observed no additive effects (The Cooperating Clinics Committee of the Amer. Rheum. Assn., Clin. Pharmacol. Ther., 8:11, 1967).

*Rheumatoid (ankylosing) spondylitis.*—Although adequate trials are lacking, indomethacin appears to be as effective as phenylbutazone in ankylosing spondylitis. For patients in whom aspirin is ineffective, some clinicians prefer indomethacin to phenylbutazone because its side effects, while frequent, are not likely to be as serious as they may be with phenylbutazone; many deaths from blood dyscrasias have followed prolonged or repeated use of that drug.

*Gout.*—Indomethacin is often effective in the treatment of acute gouty arthritis (P. L. Boardman and F. D. Hart, Practitioner, 194:560, 1965), with some reports indicating that it acts more rapidly than colchicine or phenylbutazone. Some clinicians prefer a brief course of phenylbutazone, and consider both drugs preferable to colchicine because of the frequency and severity of gastrointestinal side effects with colchicine. Trials comparing indomethacin with phenylbutazone are too few to permit a confident choice between the drugs.

*Osteoarthritis.*—The manufacturer claims that indomethacin is effective in osteoarthritis of the hip. While the evidence is not conclusive, one controlled short-term trial does support this claim (J. Wanka and A. St. J. Dixon, Ann. Rheum. Dis., 23:288, 1964). Present evidence does not adequately support the results of early studies showing the drug to be effective in other joints affected by osteoarthritis.

*Adverse effects.*—The incidence of adverse effects has varied, in different studies, from a few per cent to about three-quarters of the patients. Gastric side effects have been less frequent with the capsule formulation which replaced the early tablet formulation. Most of the studies have shown a high incidence of such side effects as headaches, vertigo, and gastrointestinal disturbances, including nausea and vomiting. Peptic ulceration has occurred, sometimes with bleeding, and cholestatic jaundice has been reported. Mental depression has also been reported (M. Thompson and J. S. Percy, Brit. Med. J., 1:80, 1966). There have been a few reports of leukopenia, thrombocytopenia, and agranulocytosis. A number of deaths have been associated with the use of indomethacin, some of them the result of ulceration and bleeding. Both the incidence and the severity of side effects have usually been dose-related. Indomethacin may interfere with resistance to infection, particularly in children (J. C. Jacobs, JAMA, 199:932, 1967), or may activate latent infections. For the present, indomethacin should not be administered to children.

*Dosage.*—The manufacturer recommends an initial dosage of 50 to 75 mg a day with gradual increases up to 200 mg a day. Because of the high incidence of adverse effects at 200 mg many clinicians limit dosage to 100 to 150 mg a day.

*Conclusion.*—Indomethacin appears to be no more effective than aspirin in the treatment of rheumatoid arthritis; all Medical Letter consultants agree that aspirin is the drug of choice and that indomethacin should be used only in patients who cannot tolerate aspirin. There is some belief that the combination of indomethacin and aspirin may be beneficial in a few patients with rheumatoid arthritis not satisfactorily controlled on aspirin alone, and that a trial of the combination in such patients is worthwhile. Indomethacin appears to be as effective as phenylbutazone in the treatment of ankylosing spondylitis and is probably less hazardous. It is also effective in acute gouty arthritis, and it may be helpful in the treatment of osteoarthritis of the hip. Despite frequent minor side effects and occasional serious effects, indomethacin appears to be less hazardous for long-term use than corticosteroids, gold, or phenylbutazone.

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[From the Medical Letter, vol. 7, No. 22, Oct. 22, 1965]

#### INDOCIN

Indomethacin (Indocin—Merck) is a nonsteroid indole derivative offered for the treatment of rheumatoid arthritis, ankylosing (rheumatoid) spondylitis, osteoarthritis and gouty arthritis. Like other drugs used in arthritis—aspirin, phenylbutazone, and the corticosteroids—indomethacin has analgesic and anti-inflammatory effects. The drug is not free of serious side effects, and its effectiveness is much more limited than many of the early claims would indicate; nevertheless, it appears to be a useful addition to the group of drugs available; for the treatment of arthritic disorders.

*Rheumatoid arthritis and spondylitis.*—In a number of clinical trials, mostly uncontrolled, about 40 to 50 per cent of patients with rheumatoid arthritis showed some improvement when given indomethacin. In one study, doses of 150 to 200 mg of indomethacin daily were found to be effective in most patients with mod-

erately severe rheumatoid arthritis, though they had little effect when the disease was severe (A. M. Marmont et al., in International Symposium on Non-Steroidal Anti-Inflammatory Drugs, Amsterdam, Excerpta Medica Foundation, 1965, p. 363). In ankylosing spondylitis, indomethacin has appeared to relieve pain more consistently than in other types of arthritis (F. D. Hart and P. L. Boardman, Brit. Med. J., 2:965, 1963). How it compares with aspirin and phenylbutazone in the treatment of spondylitis is not yet known.

Indomethacin has been used in combination with prednisone in a number of studies on patients with rheumatoid arthritis. The use of indomethacin permitted reduction of dosage of the steroid with all the patients in some studies, with fewer than half in others. The side effects of corticosteroids are much more serious than those thus far observed with indomethacin, and the combination, with reduced dosage of steroids, is well worth a trial where steroids cannot be eliminated altogether. It is not yet known whether indomethacin can be safely and effectively used in combination with such other anti-rheumatic drugs as phenylbutazone, gold salts and chloroquine.

*Gouty arthritis.*—In the treatment of acute gouty arthritis with indomethacin, many patients have shown improvement within about 48 hours (P. L. Boardman and F. D. Hart, Practitioner, 194:560, April, 1965). How the drug compares in effectiveness with colchicine and phenylbutazone can be determined only by better-controlled trials than those so far reported. The usefulness of indomethacin combined with a uricosuric agent such as probenecid (Benemid—Merk) in the treatment of chronic gouty arthritis is being investigated.

*Osteoarthritis and other conditions.*—In uncontrolled trials, indomethacin has been reported to be effective in relieving pain in osteoarthritis. A valid judgment of its usefulness must await further trials. It is not recommended by the manufacturer for such acute musculoskeletal disorders as bursitis, tendinitis, and synovitis.

*Adverse effects.*—Adverse effects, often severe, and requiring discontinuance of the drug in many patients, are common, and a few fatalities have been attributed to indomethacin. Among the most frequent adverse effects are headache, dizziness, gastrointestinal disturbances (nausea, anorexia, vomiting, diarrhea, bleeding and ulceration), and psychic disturbances. Whether significant hematologic, renal hepatic, or neurologic reactions occur is not clear. A fuller assessment of adverse effects will be possible only after longer use; indomethacin appears to be too hazardous to be substituted for aspirin when that drug is effective, but it may prove less hazardous than other anti-arthritis drugs.

*Precautions and contraindications.*—The manufacturer warns that indomethacin is contraindicated in patients with active peptic ulcer, gastritis, ulcerative colitis, and regional ileitis. Whether it crosses the placental barrier is not yet known, nor are its effects on the human fetus; therefore, indomethacin should not be used in pregnant women. The manufacturer also warns that there has been insufficient experience to warrant its use in children. Because of the frequency of dizziness, lightheadedness, and feelings of detachment, patients on indomethacin should be cautioned against operating motor vehicles or other machinery, climbing ladders, etc., and the drug should be used with great caution in patients with psychological difficulties, epilepsy or parkinsonism, since it sometimes aggravates these conditions.

*Dosage and administration.*—The recommended initial dose is 25 mg twice daily, with gradual increase as needed. Good response is often obtained with 100 mg daily, divided into four doses. Further improvement rarely occurs when the dose is increased above 150 or 200 mg a day. The drug should be given with food to reduce gastric irritation.

*Conclusion.*—Early clinical trials indicate that indomethacin is a useful addition to the group of drugs available for the treatment of rheumatoid arthritis and ankylosing spondylitis. Its place in the management of acute gouty arthritis and osteoarthritis is less clear; properly controlled trials are needed.

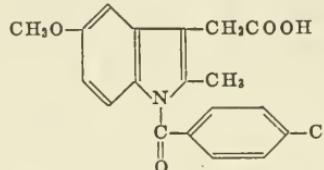
In the treatment of rheumatoid arthritis, aspirin is still the drug of first choice (see The Medical Letter, Vol. 7, p. 75, 1965, for a discussion of the side effects of aspirin). When effective doses of aspirin are not well tolerated, indomethacin may be used with lower doses of aspirin or, if necessary, substituted for it, before resort is had to corticosteroids. In patients already on corticosteroids, reduction of the steroid dosage and a decrease in steroid side effects can often be achieved by the addition of indomethacin.

If gastric ulceration occurs with either aspirin, phenylbutazone, or corticosteroids, indomethacin cannot be considered a safe substitute since it, too, causes gastric ulceration. In such cases, gold salts or chloroquine can be tried; these also have serious side effects, but they do not cause gastric ulceration.

[From New Drugs, 1967, pp. 539-542]

## INDOMETHACIN

## [INDOCIN]

1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid

## ACTIONS AND USES

Indomethacin is a new type of nonsteroidal chemical compound that has anti-inflammatory, antipyretic, and analgesic properties.

Present clinical experience indicates that this drug is as effective as the salicylates in patients with rheumatoid arthritis. However, its use is not necessary when salicylate therapy is effective. Although aspirin is still considered the drug of first choice, indomethacin may be tried if aspirin ceases to be beneficial or is no longer tolerated. Doses of aspirin may be taken in between regular doses of indomethacin if necessary.

When given alone, indomethacin is more effective in active rheumatoid arthritis than in the inactive "burnt-out" type. In about two-thirds of the patients, pain, tenderness, and stiffness decrease and ambulation increases in two to three days. However, some clinicians have found that maximal benefits are not obtained until indomethacin has been given for a month or more. With prolonged administration, 10% to 15% of the patients who responded initially must stop taking indomethacin because of its untoward effects.

It has been reported that indomethacin reduces joint swelling and edema in some patients with rheumatoid arthritis. However, results have been equivocal in the few studies in which objective measurements of joint size were made. The erythrocyte sedimentation rate was not affected.

When given alone, indomethacin is less effective than the corticosteroids in the treatment of rheumatoid arthritis. When given concomitantly, however, the dose of the steroids often can be halved and in some patients completely withdrawn. Thus, indomethacin may be especially useful in patients who have been receiving long-term therapy with corticosteroids. However, the hazards of combined therapy with steroids and indomethacin have yet to be fully evaluated.

Indomethacin has been particularly useful in the treatment of mild to moderate osteoarthritis of the hip joint, a condition that is resistant to all other anti-inflammatory agents. It also appears to relieve the pain of ankylosing spondylitis as effectively as does phenylbutazone.

Indomethacin produces anti-inflammatory effects in patients with gout and may be as effective as phenylbutazone in its promptness of action and the degree of relief it provides. Because it has produced relief in acute attacks within 48 hours, and because it lacks the untoward effects of colchicine, some clinicians consider it to be the drug of choice for these attacks; however, controlled trials are needed to determine how its effectiveness compares with that of colchicine. Indomethacin may be useful as a supplement to colchicine in the management of severe cases of gout. Whether it is useful as a prophylactic agent in gouty arthritis remains to be established.

This drug should not be used in children until the indications for use and appropriate dosage have been established.

## ADVERSE REACTIONS

Central nervous system effects (headaches, usually severe in the morning; vertigo; light-headedness; mental confusion) occur during the early weeks of therapy in about 20% to 30% of patients taking indomethacin. Drowsiness, convulsions, depression, and psychic disturbances such as depersonalization have also been reported. Generally, these effects are dose-related and are less likely to appear if the daily dosage is 100 mg. or less given in divided amounts. The symptoms may occur within the first few hours after administration or may be

delayed for two or three days; they frequently disappear with continued use but, if they are severe, the drug should be discontinued.

Gastrointestinal reactions (nausea, indigestion, epigastric burning, stomatitis, diarrhea), which have been observed in about 25% of the patients, often are transient and can be minimized by giving the drug after meals and with milk at bedtime. These symptoms are severe enough to require discontinuing the drug in less than 10% of the patients but, even in these, the adverse effects may not recur when administration of the drug is resumed.

Indomethacin should be regarded as being potentially ulcerogenic. It may produce single or multiple ulceration of the esophagus, stomach, duodenum, or small intestine. Cases of perforation and hemorrhage, a few of them fatal, have been reported. Some patients with a history of peptic ulcer have tolerated the drug without experiencing gastrointestinal symptoms or having evidence of an active ulcer; other patients have developed ulcers after having taken the drug for 1½ to 3 years. Since most patients who developed ulcers had received doses of 150 to 300 mg. a day, dosage may well be a contributing factor. Occult bleeding and resulting anemia may occur in the absence of an ulcer, and persistent indigestion may be a symptom of this. Although measurements indicate that the occult blood loss associated with indomethacin is less than that produced by clinically equivalent doses of aspirin, hemoglobin determinations should be made regularly and the drug should be discontinued if any evidence of gastrointestinal bleeding develops.

Leukopenia, purpura, and thrombocytopenia may develop. Agranulocytosis has been reported rarely, but its relationship to indomethacin administration has not been established. Reports of jaundice and hepatitis have also appeared.

Dermatologic or hypersensitivity-type reactions (pruritus, urticaria, rash, angioneurotic edema, loss of hair, acute respiratory distress) and reactions affecting the eye or ear (tinnitus, blurred vision, orbital and periorbital pain) have occurred infrequently.

No significant alterations in the glucose tolerance test, electrolyte balance, or kidney function have occurred after administration of indomethacin for periods as long as three years. However, more long-term studies are needed to completely assess the effects of its prolonged use.

#### PRECAUTIONS

Patients who require larger dosages of indomethacin must be observed more closely for the possible occurrence of toxic effects. The patient may accept the untoward effects of indomethacin if he is told of their possible occurrence. Indomethacin, like aspirin, should be administered on a regular schedule and not used indiscriminately in the treatment of rheumatoid arthritis.

Indomethacin is contraindicated in patients with active peptic ulcer, gastritis, regional enteritis, or ulcerative colitis, and it should be used with caution in patients with a history of these disorders. These patients may tolerate the drug if small doses are used. Indomethacin also should be used with care in patients who have epilepsy, parkinsonism, or emotional or psychiatric problems, since the drug may aggravate these conditions.

Because of the possible occurrence of central nervous system effects, patients being given indomethacin should avoid activities requiring mental alertness, judgment, or physical coordination (e.g., driving a car, operating dangerous machinery), particularly during the early weeks of therapy.

Indomethacin is contraindicated in patients with asthma who are sensitive to aspirin.

It is now known that indomethacin can mask the signs and symptoms which usually accompany infectious disease. Therefore, the physician must be aware of this possibility to avoid delay in the treatment of an infection, and should use the drug with caution in the presence of existing, controlled infections.

No teratogenic effects have been demonstrated in animal studies. However, it has been shown that indomethacin does cross the placental barrier. Thus, the possibility of risk to the fetus must be weighed against the expected therapeutic benefits if indomethacin is considered for administration to a pregnant woman.

A few deaths in children with severe juvenile rheumatoid arthritis who were receiving indomethacin with other drugs have been reported; in two of these cases, death was attributed to intercurrent infections of possibly unrecognized severity. Clinical studies have been insufficient to establish any recommendation for the use of indomethacin in infants and children and, at the present time, the drug is considered to be *contraindicated in infants and children* because safe conditions for use have not been established.

## PHARMACOLOGY

In man, indomethacin is absorbed promptly following oral administration, and peak plasma levels occur within two hours. About 90% of a single dose is excreted in 24 to 48 hours; approximately two thirds of this amount is excreted in the urine as the glucuronide and the remainder is excreted in the feces.

## DOSAGE AND PREPARATIONS

*Route of administration.*—Oral.

*Dosage.*—To minimize adverse reactions, small doses of indomethacin are given initially; when necessary, the size of the dose is then gradually increased until an effective level is reached.

In *rheumatoid arthritis*, *ankylosing spondylitis*, and *degenerative joint disease of the hip*, the initial dose is 25 mg. two or three times daily. If the patient does not respond, this dose is increased at weekly intervals by increments of 25 mg. a day until a satisfactory response is obtained or until a daily dose of 150 to 200 mg. is reached; larger doses are not recommended. If adverse reactions occur, the drug should be discontinued or successive adjustments in dosage should be made until the best possible response is obtained. After an acute phase or exacerbation of rheumatoid arthritis is controlled, the dose of indomethacin should be reduced to a satisfactory maintenance level. No reports on its occasional intermittent use for short periods are available.

When indomethacin is added to a regimen of corticosteroid therapy, it is often possible to reduce the dose of the steroid by as much as one half or to discontinue it entirely. However, this reduction should be made gradually in order to avoid the effects of steroid withdrawal.

Acute attacks of *gout* may be controlled with a dosage of 50 mg. three times a day until the attack subsides. During the intervals between attacks, a dose of 25 mg. twice a day may be sufficient.

*Preparations.*—Capsules 25 mg.

*Supplied by.*—Merck Sharp & Dohme [Indocin].

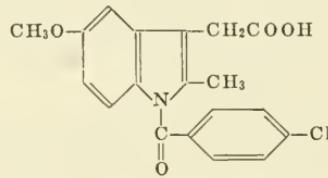
Year of introduction: 1965.

Evaluated for N.D. 1966. Reviewed: 1967.

[From New Drugs, 1966, pp. 531-534]

## INDOMETHACIN

## [INDOCIN]



1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid

## ACTIONS AND USES

Indomethacin is a new type of nonsteroidal chemical compound that has anti-inflammatory, antipyretic, and analgesic properties.

Present clinical experience indicates that this drug is as effective as the salicylates in patients with rheumatoid arthritis. However, its use is not necessary when salicylate therapy is effective. Although aspirin is still considered the drug of first choice, indomethacin may be tried if aspirin ceases to be beneficial or is no longer tolerated. Doses of aspirin may be taken in between regular doses of indomethacin if necessary.

When given alone, indomethacin is more effective in active rheumatoid arthritis than in the inactive "burnt-out" type. In about two thirds of the patients, pain, tenderness, and stiffness decrease and ambulation increases in two to three days.

However, some clinicians have found that maximal benefits are not obtained until indomethacin has been given for a month or more. With prolonged administration, 10% to 15% of the patients who responded initially must stop taking indomethacin because of its untoward effects.

It has been reported that indomethacin reduces joint swelling and edema in some patients with rheumatoid arthritis. However, results have been equivocal in the few studies in which objective measurements of joint size were made. The erythrocyte sedimentation rate was not affected.

When given alone, indomethacin is less effective than the corticosteroids in the treatment of rheumatoid arthritis. When given concomitantly, however, the dose of the steroids often can be halved and in some patients completely withdrawn. Thus, indomethacin may be especially useful in patients who have been receiving long-term therapy with corticosteroids. However, the hazards of combined therapy with steroids and indomethacin have yet to be fully evaluated.

Indomethacin has been particularly useful in the treatment of mild to moderate osteoarthritis of the hip joint, a condition that is resistant to all other anti-inflammatory agents. It also appears to relieve the pain of ankylosing spondylitis as effectively as does phenylbutazone.

Indomethacin produces anti-inflammatory effects in patients with gout and may be as effective as phenylbutazone in its promptness of action and the degree of relief it provides. Because it has produced relief in acute attacks within 48 hours, and because it lacks the untoward effects of colchicine, some clinicians consider it to be the drug of choice for these attacks; however, controlled trials are needed to determine how its effectiveness compares with that of colchicine. Indomethacin may be useful as a supplement to colchicine in the management of severe cases of gout. Whether it is useful as a prophylactic agent in gouty arthritis remains to be established.

#### ADVERSE REACTIONS

Central nervous system effects (headaches, usually severe in the morning; vertigo; light-headedness; mental confusion) occur during the early weeks of therapy in about 20% to 30% of patients taking indomethacin. These symptoms may occur within the first few hours after administration or may be delayed for two or three days; they frequently disappear with continued use and are reversible when the drug is discontinued. Generally, these effects are dose-related and are less likely to appear if the daily dosage is 100 mg. or less given in divided amounts.

*Gastrointestinal reactions* (nausea, indigestion, epigastric burning, stomatitis, diarrhea), which have been observed in about 25% of the patients, often are transient and can be minimized by giving the drug after meals and with milk at bedtime. These symptoms are severe enough to require discontinuing the drug in less than 10% of the patients but, even in these, the adverse effects may not recur when administration of the drug is resumed.

Indomethacin should be regarded as potentially ulcerogenic, although the available evidence on this point is contradictory. Some patients with a history of peptic ulcer have tolerated the drug without experiencing gastrointestinal symptoms or having evidence of an active ulcer; other patients have developed ulcers after having taken the drug for 1½ to 3 years. Since most patients who developed ulcers had received doses of 150 to 300 mg. a day, dosage may well be a contributing factor. Occult bleeding and resulting anemia may occur in the absence of an ulcer; persistent indigestion may be a symptom of this. Although measurements indicate that the occult blood loss associated with indomethacin is less than that produced by clinically equivalent doses of aspirin, hemoglobin determinations should be made regularly and the drug should be discontinued if any evidence of gastrointestinal bleeding develops.

No significant hematologic reactions or alterations in the glucose tolerance test, electrolyte balance, or liver and kidney function have occurred after administration of indomethacin for periods as long as three years. However, more long-term studies are needed to completely assess the effects of its prolonged use.

Other adverse effects reported infrequently are edema; psychic reactions such as depression; angioneurotic edema; drowsiness; tinnitus; blurred vision; and dermatologic reactions such as pruritus, urticaria, and rash. Indomethacin should be discontinued if these reactions occur. Leukopenia has been reported in a few patients.

## PRECAUTIONS

Patients who require larger dosages of indomethacin must be observed more closely for the possible occurrence of toxic effects. The patient may accept the untoward effects of indomethacin if he is told of their possible occurrence. Indomethacin, like aspirin, should be administered on a regular schedule and not used indiscriminately in the treatment of rheumatoid arthritis.

Although there is no definite evidence that indomethacin causes peptic ulcers, it is contraindicated in patients with active ulcers. In addition, because of its potential for causing bleeding in the gastrointestinal tract, the drug should be used with caution if there is a history of ulcer, regional ileitis, gastritis, or ulcerative colitis. Patients with these conditions may tolerate the drug if small doses are used. Indomethacin also should be used with care in patients who have epilepsy, parkinsonism, or emotional or psychiatric problems. Since the drug may cause aggravation of these conditions.

Because of the possible occurrence of central nervous system effects, patients being given indomethacin should avoid activities requiring mental alertness, judgment, or physical coordination (e.g., driving a car, operating dangerous machinery), particularly during the early weeks of therapy.

No teratogenic effects have been demonstrated in animal studies. However, it has been shown that indomethacin does cross the placental barrier. Thus, the possibility of risk to the fetus must be weighed against the expected therapeutic benefits if indomethacin is considered for administration to a pregnant woman. Clinical studies have been insufficient to establish any recommendation for the use of indomethacin in infants and children.

## PHARMACOLOGY

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## DOSAGE AND PREPARATIONS

*Route of Administration.*—Oral.

*Dosage.*—To minimize adverse reactions, small doses of indomethacin are given initially; when necessary, the size of the dose is then gradually increased until an effective level is reached.

In *rheumatoid arthritis*, *ankylosing spondylitis*, and *degenerative joint disease of the hip*, the initial dose is 25 mg. two or three times daily. If the patient does not respond, this dose is increased at weekly intervals by increments of 25 mg. a day until a satisfactory response is obtained or until a daily dose of 150 to 200 mg. is reached; larger doses are not recommended. If adverse reactions occur, the drug should be discontinued or successive adjustments in dosage should be made until the best possible response is obtained. After an acute phase or exacerbation of rheumatoid arthritis is controlled, the dose of indomethacin should be reduced to a satisfactory maintenance level. No reports on its occasional intermittent use for short periods are available.

When indomethacin is added to a regimen of corticosteroid therapy, it is often possible to reduce the dose of the steroid by as much as one half or to discontinue it entirely. However, this reduction should be made gradually in order to avoid the effects of steroid withdrawal.

Acute attacks of *gout* may be controlled with a dosage of 50 mg. three times a day until the attack subsides. During the intervals between attacks, a dose of 25 mg. twice a day may be sufficient.

*Preparations.*—Capsules 25 mg.

*Supplied by.*—Merck Sharp & Dohme [Indocin].

Year of introduction: 1965.

Evaluated for N.D. 1966.

[From the Washington Post, Jan. 21, 1967]

### FDA IS PROBING MERCK DIVISION

FIRM COULD FACE CRIMINAL PROSECUTION OVER AD FOR ARTHRITIS DRUG

(By Morton Mintz)

The maker of Indocin, a drug widely prescribed for arthritic disorders, has appeared at a closed hearing to show cause why the company should not be criminally prosecuted for an Indocin advertisement.

The firm, Merck, Sharp & Dohme, a division of Merck & Co., Inc., confirmed that an informal hearing was held recently by the Food and Drug Administration's district office in Philadelphia. The company said comment on the substance of the discussion would be inappropriate.

The advertisement appeared several times last year in the Journal of the American Medical Association. Its headline said Indocin (indomethacin) "extends the margin of safety in long-term management of arthritic disorders."

#### CITED BY FDA COUNSEL

That headline was cited last October by William W. Goodrich, FDA's chief counsel, in a speech in Manhattan.

"There is not yet enough experience to support the claim for greater long-term safety," he told the Pharmaceutical Advertising Club. "To the contrary, the longer the drug is used, the more side-effect information appears."

Goodrich mentioned Indocin in the course of criticizing promotions of the "Big Eight" prescription drugs—a group of drugs and antibiotics, including indomethacin, that entered the market in 1965 and within 12 months had become among the 200 drugs most frequently prescribed.

Like most new drugs, the official said, Indocin was asserted to be safer and more effective than existing products in the same therapeutic group. But as experience has accumulated, he said, "more side effects have been noted and more warning information has been required."

In response to an inquiry, FDA said it knows of 16 deaths and 303 side reactions among Indocin patients.

#### ASSOCIATION WITH DRUG

Seven of the dead were children, the agency said. Only one of these deaths was said to have had a clear-cut association with Indocin. In another, the association was regarded as questionable. In the remainder, it was regarded as dubious, because the children had had severe illnesses and had been treated with other medicines.

The nine adults had had long-standing rheumatoid arthritis and were, FDA said, in an age group over 50. The deaths of three of them were said by FDA to have had a "possibly clear-cut" relation with Indocin. Such a relation was doubted in the others, all of whom had had major, pre-existing complications.

In another complaint about the AMA Journal ad for Indocin, Goodrich told the Advertising Club that the ad quoted "authoritative sources, without the full impact of the actual articles."

He pointed to a claim of usefulness for Indocin in arthritis of the spine ("anklosing spondylitis"). The claim is supported by a reference. A physician who checked it out, Goodrich said, would find that the reference was to a 2-inch abstract of a speech made in 1964.

In addition, Goodrich said, the ad failed to cite this statement in the abstract: "Excellent results have also been obtained in some cases of rheumatoid arthritis . . . there have been some striking failures as well."

A third complaint made by the agency counsel was that the ad "omits some very important warning information that is required" in the authorized prescribing instruction—the brochure enclosed with every package of a drug.

In West Point, Pa., a Merck, Sharp & Dohme spokesman said:

"It is our judgment, based on the facts of Indocin use, that this new anti-arthritis agent does not suffer from certain disadvantages such as the production of hormonal side effects and certain blood dyscrasias which do occur with some of the other agents previously available. In this way it has extended the margin of safety in the long-term management of arthritic disorders."

Since the Goodrich speech FDA has refused to comment on the closed hearing or on the possibility of prosecution. Except where data are requested by Congress,

the agency customarily makes no disclosure to the medical or lay public when it calls and holds such hearings or takes certain other steps against drug ads that it considers misleading.

#### POSSIBLE ACTIONS

In the pending case, FDA's Philadelphia office could recommend anything from concurrence with a company position that it had done nothing wrong to prosecution. A recommendation for a criminal proceeding could be vetoed at headquarters in Washington or by the Justice Department if the case were to be sent there.

Goodrich disclosed in his October speech that a few days earlier Indocin's maker had mailed "a new revised brochure to the profession with new cautionary information in heavy print." The fatalities among Indocin patients were mentioned neither in the brochure nor in the accompanying "Dear Doctor" letter signed by Dr. Frederick K. Heath, vice president for professional communications.

Displayed on the envelope, however, was a prominent box saying "Safety/Drug Safety Information."

Generally, Dr. Heath blended an alert to "important changes" in prescribing instructions for Indocin with statements marked by a promotional tone.

His letter said that "144,000,000 patient days of therapy in 99 countries" had been accumulated with Indocin since its introduction about 16 months earlier.

He also said that Indocin "has become, next to aspirin, the most frequently prescribed antirheumatic drug." The characterization of indomethacin as an "antirheumatic drug" is no longer allowed by FDA.

In addition, the agency found the letter inadequate and insisted on a new one, which the manufacturer mailed in December. Above the "Dear Doctor" salutation the words "Drug Safety Information" were printed in deep blue. Promotional plugs for Indocin were absent.

In addition to directing attention to new precautions, Dr. Heath's December letter emphasized that Indocin "should not be prescribed for children because safe conditions for use have not been established."

That same warning appears three times in boldface type in the new prescribing circular enclosed with the letter.

Also in boldface, the circular says that severe and even fatal reactions have occurred in a few cases of severe juvenile rheumatoid arthritis in children who received Indocin along with other drugs. The precaution in the October circular about the use of Indocin in children was found by FDA to be too mild.

#### ARTICLE CRITICIZED

The Goodrich speech also contained criticism of an article by freelancers Phyllis and Robert P. Goldman in the July Pageant. The title was "INDOCIN," the trade name of the drug.

The FDA counsel said the article "featured" Indocin "for 'bursitis,' 'trick knee,' 'tennis elbow' and 'a host of other less common disorders characterized by pain and swelling in and around the joints.'"

"The only support for these claims," Goodrich said, "was user testimonials which, according to the article, were made available to the writer by the sponsor of the drug."

[From the Washington Post, Mar. 19, 1967]

#### FDA BEGINS A RESTUDY OF ARTHRITIS DRUG

SOME AUTHORIZED CLAIMS FOR INDOCIN ARE NOW IN DOUBT

(By Morton Mintz)

The Food and Drug Administration is reevaluating a drug that has been taken mainly for arthritic disorders by millions of persons here and abroad.

The drug is Indocin (indomethacin). In the United States FDA-authorized instructions to physicians prescribing the drug indicate that it is useful in rheumatoid arthritis, arthritis of the spine, degenerative joint disease of the hip and gout.

It is one or more of these authorized claims that the FDA is now reevaluating.

The FDA disclosed its action yesterday in response to a Washington Post query about articles in three prestigious medical journals about Indocin's efficacy against rheumatoid arthritis. Two of the reports indicate that aspirin is as

effective as Indocin; the third indicates the drug to be no more effective than a placebo, a pill containing an inert substance.

The reports raise questions not only about the agency's handling of Indocin, which was approved in June, 1965, but also about the law's strict requirement that "substantial evidence" of efficacy be demonstrated.

Merck & Co., the manufacturer, said Thursday that Indocin's safety and efficacy were established "by more than 300 clinical investigators" and by "a wealth" of experience.

The three journal reports were prepared by experts who performed well-controlled clinical investigations. And only selected patient groups got Indocin; other groups got aspirin, Indocin and aspirin, or aspirin and/or a placebo. These were highly sophisticated double-blind studies.

Neither patients nor physicians knew what was being administered until a code was broken at the end of the trials. Some patients were crossed over, that is, switched without disclosure from one group to another.

But Merck said some of the studies in behalf of Indocin it had submitted to the FDA also were double-blind. It also protested that Indocin worked with some rheumatoid arthritis victims with whom aspirin failed; and that in the other diseases for which Indocin is approved it allows successful control while aspirin does not.

#### VALUES IRREGULAR

In addition, the relative value of drugs in rheumatoid arthritis is hard to measure objectively, Merck said. Many patients are relieved of pain by aspirin; investigators are unwilling to substitute a placebo for test purposes, the company said.

Last October, Merck revised its prescribing brochure and mailed a copy accompanied by a letter to the Nation's practicing physicians. The letter cited "new cautionary information" but made no mention of fatalities.

By December, FDA knew of 329 adverse reactions, including seven deaths in children and nine in elderly persons. It termed the relation to Indocin unclear in one fatality, "possibly clearcut" in three others and highly questionable in the rest.

The October Merck letter said that "144,000,000 patient days of therapy" had been accumulated with indomethacin, and that it "has become, next to aspirin, the most frequently prescribed antirheumatic drug." The characterization of Indocin as "antirheumatic" was later disallowed by the FDA.

#### DEATHS CITED

In November, a jolting warning letter was sent Canadian physicians by the Food and Drug Directorate, the FDA's north-of-the-border counterpart. The letters told of several indomethacin deaths in children and of a number of unexpected adverse reactions.

These included "not uncommon" and sometimes severe effects on the central nervous system, and blood diseases and blurred vision.

In upper case, The Canadian government letter said in capitals "That Indomethacin Should Not Be Used in Children . . ." In addition, doctors were warned that the drug "can mask the signs and symptoms of an infectious process or activate a latent bacterial infection."

In Washington, the FDA called in Merck. In December the company sent out a 2-paragraph letter which warned against Indocin use in children and called attention to the enclosed prescribing brochure which had again been revised to emphasize that warning.

Several months before the FDA approved Indocin in 1965, warnings against its use were published in the Medical Journal of Australia by physicians who "detailed an imposing list of side effects."

#### SUGGESTION'S ROLE

The double-blind study, reported in the British Medical Journal last Jan. 14 involved 28 persons for 10 weeks.

Although side effects "occurred more often with indomethacin" than with a placebo, the report inferred that "suggestion played a large part in determining both the incidence and variety . . ." The authors were three Welsh physicians, Phelim Donnelly, Kenneth Lloyd and Hubert Campbell.

The New England Journal of Medicine study, published March 2 by Drs. Robert S. Pinals and Sumner Frank of Boston, was done on 24 patients for a month. Two

on Indocin, including one also taking aspirin, dropped out with "intolerable side effects." Another dropped out for an unrelated reason.

Among the remaining 21, one-third preferred aspirin and one-third indomethacin; one-third was unable to detect a difference. The physicians rated Indocin superior in five patients and aspirin in six.

#### 10 WERE THE SAME

No difference was found in 10. "Side effects did not differ in frequency or severity," but headache was noted more commonly with indomethacin and auditory symptoms with aspirin, they said.

The study reported in the January-February Clinical Pharmacology and Therapeutics was sponsored by the American Rheumatism Association and was done by biostatistician Donald Mainland, primarily to establish objective standards for judging rheumatoid arthritis drugs.

No significant differences were found among patients taking Indocin and others taking a placebo. Patients in both groups were allowed to take as much aspirin as desired. Merck cited this in asserting that the study does not show that the relative effectiveness of Indocin and aspirin used separately.

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[From the Washington Post, May 21, 1968]

#### DRUG AD EXPORTS POSE A PROBLEM

(By Morton Mintz)

In Animal Farm, the satirical fable by the late George Orwell, all the animals were equal, but only for a time. Then some animals asserted themselves to be more equal than others. A parallel may exist in the attitudes businessmen in one country take toward citizens of another when it comes to advertising prescription drugs.

American pharmaceutical companies hold a commanding position in the non-Communist world, and in promoting drugs it might be presumed that they would treat doctors abroad the same as doctors here. If a promotional claim is prohibited in this country because it might mislead a physician (and kill, injure, or at least exploit his patient), the same claim presumably would not be made in other countries. But that this is not always the case is suggested by a recent disclosure concerning Abbott Laboratories of North Chicago, Ill.

In March, 1967, this firm ran an advertisement in the *Journal of the American Medical Association* for Enduron, Abbott's trade name for a thiazide diuretic called methyclothiazide. The ad claimed that in removing excess fluids, Enduron caused a lesser depletion of potassium than rival prescription products. This claim was deemed by the Food and Drug Administration to be misleading. Under pressure by the FDA, the company then sent a letter individually to every prescribing physician in the Nation acknowledging that the loss of potassium with Enduron was not seen by experts as significantly different from the loss with other thiazide diuretics.

But a year later—in April, 1968—substantially the same claims were being made to physicians in Canada for the same product, which there is called Duretic. One ad in which this occurred was published in the *Canadian Medical Association Journal* by Abbott Laboratories Limited. Whether the claims which the parent company had repudiated were carried in other publications and in other countries, a spokesman in North Chicago refused to say.

Other incidents raising ethical questions in the same ballpark have cropped up in hearings held by the Senate Monopoly Subcommittee and troubled its chairman, Sen. Gaylord Nelson (D-Wis.). A recent one concerned indomethacin, a rheumatoid arthritis drug which Merck & Co. sells in the United States as Indocin and elsewhere as indocid. In this country, the FDA has refused to let Merck claim that the drug has been demonstrated to be safe and effective in certain additional medical conditions.

But these same medical conditions are freely promoted as appropriate for Indocid in about 100 other countries. To be sure, a few of these are highly developed Western nations which, it might be fairly argued, could have effective drug regulation if they do not now have it. What especially bothered Nelson, however, was that in countries with no regulation and no significant scientific community, drug promotion can be entirely free-wheeling, with resultant over-prescribing at the expense of the health and pocketbooks of innocent patients. In such countries, Nelson asked Merck president Henry Gadsden, "What is your standard of guidance for advertising?"

Gadsden said that his firm's standard "is whatever has been approved by the scientists of Merck as appropriate," and for which evidence has been submitted to the FDA, even if the agency has not been persuaded by that evidence. Nelson did not remind Gadsden of FDA testimony the day before that the agency's counsel was considering whether a criminal prosecution of Merck for misleading advertising of Indocin in the United States should be recommended to the Justice Department. Instead, the Senator said in regard to drug promotion in less-developed countries, ". . . there are lots of companies in this business that might not be as conscientious as Merck . . ."

Surely a difficult and delicate problem is posed. Americans may be uneasy about how American firms promote medicines abroad; they may doubt the wisdom of applying the adage about doing in Rome as the Romans do. But they cannot lightly try to arrogate unto themselves power to tell other countries what to do. Maybe other countries could require as a condition of import that advertising and promotion conform to United States requirements. Maybe it's a problem for the World Health Organization. Maybe even there is no solution.

[From the Washington Post, Mar. 3, 1968]

#### LETTER MISLEADING, DRUG FIRM ADMITS

(By Morton Mintz)

For the second time since May, Geigy Pharmaceuticals has conceded that it engaged in a prescription-drug promotion that the Food and Drug Administration criticized as "potentially misleading."

A promotional letter to physicians, the company said, "presented only favorable information" about Persantine, which is used in long term therapy of patients with the intense chest pain known as angina pectoris.

Actually, the firm acknowledged, "there is a substantial body of opinion that does not support the claimed effectiveness" of Persantine, the Geigy brand of dipyridamole. This is one of the drugs marketed before 1962 for which claims of usefulness have been neither approved nor disapproved by FDA, pending an efficacy review by the National Academy of Sciences.

The promotional letter for Persantine claimed that several studies document its effectiveness "in extending walking distance and generally increasing exercise tolerance." The claim was backed up with an enclosure—a reprint of a study reported last March in the *Journal of Chronic Diseases*.

The claim was knocked down in September, the Geigy Chemical Corp. division has recognized, by a report in the *Journal of the American Medical Association*. There, telling of a six-month, so-called double-blind study that was designed to eliminate possible bias, two researchers said:

"The study failed to detect a statistically significant difference between the improvement in patients receiving dipyridamole and the improvement in patients receiving a placebo," or inert, dummy pill.

This conclusion was relayed by Geigy in a "corrective letter" sent individually on Feb. 15 to each of the country's prescribing physicians.

Geigy went on to recall that the AMA's Council on Drugs had said last year in its primary publication that double-blind studies comparing dipyridamole with a placebo "have shown equivocal results . . . the drug has not been shown to be effective in the long-term treatment of angina pectoris . . .

"Our future promotion will express the range of expert medical opinion on the effectiveness of Persantine when any segment of that opinion" is cited in promotional material, the company said.

The earlier case involved two Geigy prescription drugs used to lower blood pressure. They are Hygroton (chlorthalidone), which the FDA said was misleadingly advertised in *MD Medical News Magazine*, and Regroton, (chlorthalidone plus reserpine), which was advertised in *Circulation Magazine* in a way also condemned by the agency.

In the earlier case the firm sent its first "corrective letter." Various firms have sent a total of 21 of them since February, 1967. Had they not been sent, FDA was prepared in each case to seize interstate shipments and announce the action in a press release.

**Senator NELSON.** We are adjourned subject to call of the Chair.

(Whereupon, at 1:55 p.m., the hearing adjourned subject to the call of the Chair.)



# COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

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TUESDAY, SEPTEMBER 17, 1968

U.S. SENATE,  
MONOPOLY SUBCOMMITTEE OF THE  
SELECT COMMITTEE ON SMALL BUSINESS,  
*Washington, D.C.*

The subcommittee met, pursuant to call, at 9:40 a.m., in room 318, Old Senate Office Building, Senator Gaylord, P. Nelson (chairman of the subcommittee) presiding.

Present: Senator Nelson.

Also present: Benjamin Gordon, staff economist; James H. Grossman, minority counsel; Elaine C. Dye, research assistant; and William B. Cherkasky, legislative director, staff of Senator Nelson.

Senator NELSON. Today the Monopoly Subcommittee of the Senate Small Business Committee resumes hearings first begun in May 1967 as part of its study of the pharmaceutical industry.

Our primary concern, during the next 4 days of hearings,<sup>1</sup> will be to explore the impact of the drug manufacturers' salesmen, commonly called detail men, upon the prescribing practices of the physician.

A study which appeared in the Canadian Medical Journal in April 1968, the American Medical Association's study conducted some years ago, and testimony before our subcommittee indicated that oral statements by drug manufacturers' detail men, who contact physicians directly, are the most potent force in promoting the use of drugs. Mr. William Goodrich, FDA's Chief Counsel, feels that the FDA has authority over the claims made by detail men under the labeling provisions of the Food, Drug, and Cosmetic Act. The American Law Division of the Library of Congress has a different opinion which I shall insert at the appropriate place in the written proceedings of these hearings.<sup>2</sup>

While section 502 of the act (21 U.S.C. 352) gives the FDA authority over written advertisements, it is not clear whether or not FDA has authority over oral representations. In any case, it would be extremely difficult, if not impractical, to monitor what thousands of detail men say to physicians.

Hence, it is difficult to avoid the conclusion that the representations of the detail men, the most important source of information for the physician, are outside the practical application of our food and drug laws.

How, then, is the public to be protected?

Can salesmen, representing commercial drug interests, be expected to act in the interests of the public?

<sup>1</sup> Testimony for September 18, 19, and 25, 1968, appears in Competitive Problems in the Drug Industry, Part 9.

<sup>2</sup> See p. 3517, *infra*.

How can we insure that the information the physician receives on drugs via word of mouth conforms with the FDA's requirements on package inserts and printed advertisements of these same drugs?

These are some of the questions we hope to consider over the next several days.

Today, we shall direct our attention to the drug Indocin. On May 3, Mr. Henry W. Gadsden, president of Merck, testified as follows:

(Merck) seeks to make sure that the marketing profile of a drug corresponds in every respect to its medical profile. \* \* \* It is Merck's policy to avoid the possibility of including any questionable statement or theme in any of our advertising or promotion. \* \* \* Our internal procedures require that every piece of advertising and promotion must have the approval of a physician and a lawyer, who are responsible for its medical accuracy and conformity with the law. \* \* \*

Testimony by the FDA indicated that these statements by the President of Merck were not in accord with reality. In fact, the FDA's Bureau of Medicine recommended prosecution of Merck for false and misleading advertising.

It was obvious that Merck's journal advertisement, submitted by the FDA as exhibits, made claims beyond those authorized in the package inserts.

In addition, the Merck Co., according to FDA's testimony on May 2, turned a "Dear Doctor" remedial letter into a promotional piece. FDA then directed Merck to send a second letter to correct the first. This kind of activity on the part of any drug company should not be tolerated by the FDA, and it is difficult, indeed, to conclude that Indocin's marketing profile, as Mr. Gadsden put it, corresponded in every respect with its medical profile.

What have the detail men been telling doctors about Indocin? I suspect that neither the FDA nor any of us here know. We do know, however, that Merck's promotional instructions to their detail men suggested uses not approved by the FDA and this is the subject of today's hearing.

On May 20, 1968, I sent the following letter to the Commissioner of the Food and Drug Administration:

I am enclosing a number of instruction bulletins on Indocin sent to Merck and Company's detail men, apparently by the district supervisor in one of the firm's sales regions.

Without attempting to interpret the law, it appears that these instructions seek to promote use of Indocin which you have not authorized.

It would be greatly appreciated if the relevant officials in your agency would examine these bulletins and send me their comments on the accuracy of the claims made and the effect on medical practice of the selling techniques recommended.

Your cooperation is greatly appreciated.

On June 17 I received an answer from the FDA, which I shall put into the record in its entirety at this point.

(The information referred to follows:)

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,  
FOOD AND DRUG ADMINISTRATION,  
Washington, D.C., June 17, 1968.

Hon. GAYLORD NELSON,  
Chairman, Subcommittee on Monopoly, Select Committee on Small Business,  
U.S. Senate, Washington, D.C.

DEAR SENATOR NELSON: This is in reply to your letter of May 20, 1968, enclosing a number of bulletins addressed to Western District Sales Associates of Merck Sharp and Dohme, Division of Merck and Company, Inc.

The Bulletins titled "Profit Improvement Promotional Program—'Indocin,'" are in memorandum form. Their form and contents would suggest that they are internal communications that are not intended to be distributed beyond the control of the firm.

These instructions to the detail force for increasing sales of Indocin recommend methods typical in the promotion of a variety of products with no public health implications. We regard the instructions as seriously misleading.

While there is considerable repetition (which in itself is a promotional tool) throughout the bulletins, the latter can be grouped for comparison into two time periods. For example, Indocin Bulletins 83, 84, 87, 88, 93 and 95 are dated between July 12 and August 4, 1965 (the period of introduction of the drug); and Indocin Bulletins 23, 66, 74, 80 and 85 are dated between April 5 and September 27, 1967.

The 1965 bulletins suggest generally to the detail men that they promote use of Indocin beyond approved indications, and play down side effects and other warnings present in the labeling. Some examples of passages from the bulletin are:

#### *Uncwarranted Extension of Indications*

"... when there is Heat . . . Redness . . . Swelling . . . and Pain in the muscles or joints . . . 'Indocin' is usually effective."

"... treatment of the misery inflicted by arthritic diseases."

"Available to relieve pain, reduce fever tenderness and swelling, and increase joint mobility in patients with rheumatic disorders."

"... Just Plain musculoskeletal Aches and Stiffness . . ."

In connection with the above, Bulletin 87 contains this admission:

"In fact, our guys are using a real expanded claim for 'Indocin' on inflammation. They are consistently telling their doctors that . . . [as above]"

#### *Deemphasis of Side Effects, etc.*

"Therapy with 'Indocin' is safer . . . a remarkable record of safety." "... Side effects . . . are usually minor and seldom constitute a problem. Usually they can be controlled by simple adjustment of dosage."

"With an extended margin of safety."

In relation to severity of side effects:

"Bothersome is probably as severe an adjective as we can use to describe these effects because in most patients they are tolerable, and transient."

The discussion of contraindications omits reference to the fact that Indocin is not recommended for use in children.

#### *Special Note*

Most reprehensible and significant in indicating the firm's disregard of the patient is the following passage:

"... it is obvious that 'Indocin' will work in that whole host of rheumatic crocks and cruds which every General Practitioner, Internist, and Orthopedic Surgeon sees everyday in his practice."

As you know, there were a series of events that occurred between 1965 and 1967 which involved our dealing with the firm regarding their advertising and promotion of Indocin. Merck was cited in regard to Indocin advertising, conferences were held with the firm's management in 1966 and the Assistant General Counsel of the Department spoke publicly regarding the misleading nature of an Indocin advertisement appearing in the *Journal of the American Medical Association*, and elsewhere. With such notice, the firm did take action to correct its forms of promotion which are subject to our control.

Notwithstanding such notice, however, we find in 1967 Indocin bulletins:

The expansion of indications for open-ended uses. "Wherever there is pain, inflammation, and swelling in or around the joint with a resultant limitation of motion. . . ." [The remainder of this sentence mentions the approved indications but in context the listed indications are examples only and do not overcome the suggestion for expanded uses.]

The continued minimization of side effects and warnings. "Most of the adverse reactions which occur with 'Indocin' are common with any antirheumatic drug. They usually are transient, easily controlled, and often disappear on continued treatment." Also, "Gastric irritation can be minimized by giving the dose of 'Indocin' after meals."

While the foregoing comments are examples of things in the bulletins that have been given prominence by repetition or other emphasis, we believe that the

full misleading character of the promotional drive can be assessed only by considering the full text of the bulletins. The setting of substantial quotas and reports of sales suggest that the promotional scheme was successful. The extent to which the sales instructions were followed, or what extrapolation the Merck detail men may have given to the bulletin instructions, in their oral presentations is, of course, unknown to us. But we do know that "Indocin" has been promoted for conditions outside the approved labeling. We have no reason to doubt that the promotional instructions contributed to prescribing of the drug for unapproved uses.

We appreciate your making the bulletins available to us for examination.  
Please let us know if we may be of further assistance.

Sincerely yours,

PAUL A. PUMPIAN,  
*Director, Office of Legislative and  
Governmental Services.*

Senator NELSON. But let me quote a few passages from this letter:

The 1965 bulletins suggest generally to the detail men that they promote use of Indocin beyond approved indications, and play down side effects and other warnings present in the labeling. \* \* \*

As you know, there was a series of events that occurred between 1965 and 1967 which involved our dealing with the firm regarding their advertising and promotion of Indocin. Merck was cited in regard to Indocin advertising, conferences were held with the firm's management in 1966 and the Assistant General Counsel of the Department spoke publicly regarding the misleading nature of an Indocin advertisement appearing in the Journal of the American Medical Association, and elsewhere. With such notice, the firm did take action to correct its forms of promotion which are subject to our control. Notwithstanding such notice, however, we find in 1967 Indocin bulletins: The expansion of indications for open-ended uses. \* \* \* The continued minimization of side effects and warnings. \* \* \*

The setting of substantial quotas and reports of sales suggest that the promotional scheme was successful. The extent to which the sales instructions were followed, or what extrapolation the Merck detail men may have given to the bulletin instructions, in their oral presentations, is, of course, unknown to us. But we do know that "Indocin" has been promoted for conditions outside the approved labeling. We have no reason to doubt that the promotional instructions contributed to prescribing of the drug for unapproved uses.

We will hear now from the witness. Our witness this morning is Dr. Robert S. McCleery, Acting Deputy Director, Bureau of Medicine, Food and Drug Administration of the U.S. Department of Health, Education, and Welfare.

Dr. McCleery, we appreciate your appearance here this morning very much, and you may proceed to present your statement. I assume that you would have no objection to interruptions for questions from time to time.

Dr. McCLEERY. No, sir.

Senator NELSON. Please go ahead, Dr. McCleery.

**STATEMENT OF DR. ROBERT S. McCLEERY, ACTING DEPUTY DIRECTOR, BUREAU OF MEDICINE, FOOD AND DRUG ADMINISTRATION; ACCOMPANIED BY DR. B. HARVEY MINCHEW, ACTING DIRECTOR, BUREAU OF MEDICINE, FDA; HARRY CHADDUCK, DEPUTY DIRECTOR, DIVISION OF MEDICAL ADVERTISING, BUREAU OF MEDICINE, FDA; WILLIAM W. GOODRICH, GENERAL COUNSEL, FDA; AND MORTON M. SCHNEIDER, ASSISTANT DIRECTOR, OFFICE OF LEGISLATIVE AND GOVERNMENTAL SERVICES, FDA**

Dr. McCLEERY. Mr. Chairman, on May 2, as you mentioned, I appeared before you at your request to discuss our experience with the

advertising of Indocin that had come to our attention. Later, you made available for our review and comment a number of sales bulletins on Indocin.

These bulletins appear to have been sent to Merck detail men by the district supervisor in one of the firm's sales regions. Their form and contents suggest that they are internal communications to the detailing force, not intended for distribution beyond control of the firm.

I would like to add here, Mr. Chairman, for the record, that the following comments are based on the assumption that these are indeed statements by responsible officials of the company, and all I have to say hereafter will be based on that assumption.

Senator NELSON. You are referring to the instructions?

Dr. McCLEERY. Right.

Senator NELSON. Just so the record will be clear at this stage, a detail man sent the bulletins to us. At the top it says, "To all western district associates from H. Glassner," who is the district manager of that area, and it is these bulletins upon which we raise the questions—

Dr. McCLEERY. Right.

Senator NELSON (continuing). With the FDA, and it is on these bulletins—

Dr. McCLEERY. That we are making comments.

Senator NELSON (continuing). That you are making your comments.

Dr. McCLEERY. Yes, sir; that is correct.

Before dealing with specific features of the instructions to Merck detail men, I should point out that the methods recommended in the bulletins for increasing sales of Indocin seem typical of methods used to promote a variety of products which ordinarily do not have such serious public health implications, as does a drug like Indocin.

And on the whole we regard these sales bulletins as seriously misleading.

Senator NELSON. Doctor, may I interrupt a moment?

If the detail man did, in fact, follow the instructions in the bulletins, he would be making some claims for this drug that were not approved by the FDA; is that correct?

Dr. McCLEERY. I would say yes.

Senator NELSON. And if the doctor got his information and relied upon the detail man, he would then be using this drug for purposes not approved by the FDA; is that correct?

Dr. McCLEERY. If he were not only influenced by some of the statements here, but derived a large part of his basis for judgment on the drug, that is why we are saying that they were misleading.

Senator NELSON. You say seriously misleading in your statement.

Dr. McCLEERY. I did. The extent to which the sales instructions were followed or what extrapolation the Merck detail men may have given to the instructions in their oral presentations are unknown to us. As to the effect of the instructions on medical practice, there seems little reason to doubt that they would contribute to the prescribing of Indocin for unapproved uses.

Mr. Chairman, we found that the bulletins could be grouped for comparative study into two time periods. Six bulletins, dated between July 12 and August 4, 1965, were representative of the group of instructions issued during the period of the introduction of Indocin to the marketplace. Six other bulletins, typical of the second group, were

dated between April 5 and September 27, 1967. This latter group was after we had had discussions with the company's top management about its promotional methods. There was, nevertheless, considerable repetition of the faulty sales concepts throughout the instructions for these two time periods.

In general, the 1965 bulletins, represented by bulletins that we selected out of the total that you submitted to us, bulletins Nos. 83, 84, 87, 88, 93, and 95 suggest to detail men that they promote the use of Indocin beyond approved indications, and play down side effects and other warning information present in the then approved Indocin labeling.

I offer now for the record a copy of the Indocin package labeling that was in effect at the time the 1965 instructional bulletins were sent out to Merck detail men.

SENATOR NELSON. That will be printed in the record at this point.  
(The information referred to follows:)

A.H.F.S. Category: 92:00

Ph. 262301 .

## INDOCIN® (INDOMETHACIN)



**INDOCIN\*** (indomethacin) is a new "anti-rheumatic" drug that has anti-inflammatory, analgesic, and antipyretic activity. It has a unique chemical structure which differentiates it from the salicylates, corticosteroids, phenylbutazone-like compounds, and colchicine. Unlike corticosteroids, it has no effect on pituitary or adrenal function.

INDOCIN is an effective anti-inflammatory agent that is suitable for long term as well as short term use in adult patients of all ages. It has been found effective to relieve pain; reduce fever, swelling, and tenderness; and increase mobility in patients with rheumatic disorders.

### INDICATIONS.

INDOCIN has been found effective in the treatment of:

Rheumatoid arthritis

Rheumatoid (ankylosing) spondylitis

Degenerative joint disease (osteoarthritis) of the hip

Gout

In these conditions INDOCIN may often replace other commonly used agents such as corticosteroids, salicylates, phenylbutazone-like compounds, and colchicine.

#### Rheumatoid Arthritis

In many patients with chronic rheumatoid arthritis INDOCIN produces a significant decrease of pain and stiffness within 48 hours, while in other patients treatment must be continued longer before significant subjective relief or objective evidence of decreased joint swelling and tenderness occurs. Treatment with INDOCIN should be continued for at least a month before concluding that it has not produced significant benefit.

When a response to INDOCIN has been obtained, the daily salicylate requirements can usually be reduced and often stopped. Also, if patients have been receiving corticosteroids, the steroid dosage often can be gradually reduced by 25 to 50 per cent, and in some patients it can eventually be completely discontinued. In such instances the steroid dosage should be reduced slowly.

In acute rheumatoid arthritis, or in acute flares of chronic rheumatoid arthritis, INDOCIN will usually produce prompt improvement with relief of pain, tenderness, swelling and stiffness.

#### Rheumatoid (Ankylosing) Spondylitis

INDOCIN frequently produces marked relief of pain and improved motion of the spine within 3 to 10 days.

#### Degenerative Joint Disease (Osteoarthritis) of the Hip

INDOCIN has provided relief of pain and increased range of motion in patients with degenerative joint disease of the hip.

#### Gout

In acute attacks of gout the response to INDOCIN is usually rapid and often dramatic. Marked reduction of pain may be obtained within 2 to 4 hours. Tenderness and heat subside within 24 to 36 hours, and swelling decreases over a 3 to 5 day period.

During the interval phase of gouty arthritis, indomethacin together with adequate doses of a uricosuric agent may provide relief of pain and prevent the recurrence of acute attacks.

### CONTRAINdications

As with other anti-inflammatory agents, INDOCIN may mask the signs and symptoms of peptic ulcer. INDOCIN itself may cause peptic ulceration or irritation of the gastrointestinal tract. For these reasons it should not be given to patients with active peptic ulcer, gastritis, or ulcerative colitis, and should be used with caution if there is a history of these disorders. In 4 patients with regional enteritis treated for up to one month, and one patient treated for 6 months, INDOCIN was well tolerated. However, in view of the paucity of data, this drug should not be given to patients with regional enteritis until additional evidence of gastrointestinal tolerance is available.

Reproduction studies in mice, rats, and rabbits showed no effect on fetal development or the reproductive cycle, although in rats there was some decrease in fetal viability. Studies in mice demonstrated that INDOCIN crosses the placental barrier. Since the effects of INDOCIN on the human fetus cannot be predicted with certainty from animal studies, the safety for use in pregnant patients has not been established.

Since the experience with INDOCIN in children is limited, it is recommended that this drug should not be administered to pediatric age groups until the indications for use and dosage have been established.

\*Registered trademark of Merck & Co., Inc.

**INDOCIN®**  
(Indomethacin)

**WARNING**

Patients who suffer from dizziness, lightheadedness, or feelings of detachment on INDOCIN should be cautioned against operating motor vehicles or other machinery, climbing ladders, etc., if these symptoms are present.

INDOCIN should be used with caution in patients with psychiatric disturbances, epilepsy, or parkinsonism, since it may, in some instances, aggravate these conditions.

**PRECAUTIONS AND ADVERSE REACTIONS**

The most frequent adverse reactions associated with INDOCIN are headache, dizziness, lightheadedness, and gastrointestinal disturbances such as nausea, anorexia, vomiting, epigastric distress, abdominal pain or diarrhea. The central nervous system effects are often transient and frequently disappear with continued treatment or with a reduction of dosage. The severity of these effects may, on occasion, require stopping, therapy.

The gastrointestinal effects may be minimized by giving the drug immediately after meals or with food.

Studies in normal subjects with radioactive chromate-tagged red blood cells indicate that large doses of indomethacin (50 mg. four times a day) produce less fecal blood loss than average doses of aspirin (600 mg. four times a day). Notwithstanding, INDOCIN may cause single or multiple ulceration of the stomach, duodenum, or small intestine. There have been reports of severe bleeding and of perforation with a few fatalities. Patients may also develop gastrointestinal bleeding with no obvious ulcer formation. If gastrointestinal bleeding occurs, INDOCIN should be discontinued. In many patients with peptic ulceration a history of a previous ulcer was present or they were on concomitant steroids, salicylates, or phenylbutazone. The possible potentiation of the ulcerogenic effect of these drugs cannot be ruled out at present. In some patients there was no history of a previous ulcer and other drugs were not being given. As a result of obvious or occult gastrointestinal bleeding some patients may manifest anemia. For this reason periodic hemoglobin determinations are recommended.

Rare reports where it is not known whether the effects can be attributed to the drug include bleeding from the sigmoid colon, either from a diverticulum or without a known previous pathologic condition, and perforation of pre-existing sigmoid lesions (diverticulum, carcinoma). In other rare cases a diagnosis of gastritis has been made while INDOCIN was being given. One patient

developed ulcerative colitis and another regional ileitis while receiving INDOCIN. When INDOCIN was given to patients with pre-existing ulcerative colitis, there was an increase in abdominal pain.

Other adverse effects that have been infrequently reported include drowsiness, tinnitus, mental confusion, depression and other psychic disturbances, blurred vision, stomatitis, pruritus, urticaria, angioneurotic edema, skin rashes, and edema.

Extensive laboratory examinations have been made during treatment with INDOCIN. A slight, usually transient, increase in BUN has been reported in some patients. Although two investigators have reported apparent changes in renal function, the reliability of the techniques used was uncertain. The preponderance of evidence indicates that INDOCIN does not have an adverse effect on renal function. Nevertheless, renal function should be checked periodically in patients on long-term therapy. Patients with pre-existing renal disease have received INDOCIN without difficulty.

A few cases of leukopenia have been reported in patients with rheumatoid arthritis; leukopenia is not uncommon in this disease.

Transient elevations in alkaline phosphatase, cephalin-cholesterol flocculation, and thymol turbidity tests have been observed in some patients and, rarely, elevations of SGOT values. The relationship of these changes to the drug, if any, has not been established.

Unlike steroids, INDOCIN has not been associated with an increased incidence of infections.

As with any new drug, patients should be followed carefully to detect unusual manifestations of drug sensitivity.

**DOSAGE AND ADMINISTRATION**

INDOCIN is available as 25 mg. and 50 mg. capsules for oral use.

In chronic disorders treatment should be started with a dosage of 25 mg. two or three times a day. Starting therapy with low doses, with gradual increases when necessary, will produce maximum benefit and minimize adverse reactions. Always give INDOCIN with food or immediately after meals to reduce gastric irritation.

*Dosage Recommendations for:*

1. Rheumatoid arthritis and rheumatoid (ankylosing) spondylitis

*Initial dosage:* 25 mg. two or three times a day. If the response is not adequate, increase the daily dosage by 25 mg. at about weekly intervals until a satisfactory response is obtained or a dosage of 150 to 200 mg. a day is reached. If a satisfactory response is

**INDOCIN®**  
(Indomethacin)

not obtained with 200 mg. a day, larger doses probably will not be effective.

If adverse reactions develop as the dosage is increased, decrease to a tolerated level and maintain at that dosage for 3 to 4 weeks. If an adequate response has not then been obtained, gradually increase the daily dosage by 25 mg. at about weekly intervals to 150 to 200 mg. a day.

For patients with acute rheumatoid arthritis or with acute flares of chronic rheumatoid arthritis, increase the dosage daily by 25 mg. until a satisfactory response is obtained or a total daily dosage of 150 to 200 mg. is reached. If adverse effects develop as the dosage is increased, it should be reduced to a tolerated level for 2 or 3 days and then gradually increased by 25 mg. every few days as tolerated. After the acute phase is under control, it is often possible to reduce the daily dosage of INDOCIN gradually to 75 to 100 mg.

*Reduction of steroid dosage:* Use of INDOCIN often will permit a gradual reduction of steroid dosage by 25 to 50 per cent. In some patients steroids can be slowly discontinued over a period of several weeks or months. The usual precautions should be observed in withdrawing steroids.

#### 2. Degenerative Joint Disease (Osteoarthritis) of the Hip

*Initial dosage:* 25 mg. two or three times a day. If the response is not adequate, increase the daily dosage by 25 mg. at about weekly intervals until a satisfactory response is obtained or a dosage of 150 to 200 mg. a day is reached. If a satisfactory response is not obtained with 200 mg. a day, larger doses will probably not be effective.

If adverse reactions develop as the dosage is increased, decrease to a tolerated level and maintain at that dosage for 3 to 4 weeks. If an adequate response has not then been obtained, gradually increase the daily dosage by 25 mg. at about weekly intervals to 150 to 200 mg. a day.

#### 3. Gout

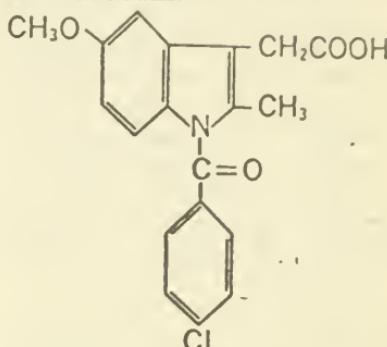
*To control acute attacks:* 50 mg. three times a day until all signs and symptoms subside. Definite relief of pain has been reported within 2 to 4 hours. Tenderness and heat usually subside in 24 to 36 hours, and swelling gradually disappears in 3 to 5 days.

*To prevent acute attacks:* During the interval phase of gouty arthritis the dosage may be reduced to as little as 25 mg. twice a day, given with an adequate dose of a uricosuric agent such as probenecid.

#### CHEMISTRY AND PHARMACOLOGY

The chemical name for indomethacin is 1-(*p*-chlorobenzoyl)-5-methoxy-2-methyl-

indole-3-acetic acid. It has the following structural formula:



#### Anti-Inflammatory Action

In laboratory animals, INDOCIN is a potent anti-inflammatory compound. Results of granuloma inhibition tests in rats receiving the compound either orally or by local application indicated activity about 85 times that of phenylbutazone. Given orally, the compound was about 4 times as active as hydrocortisone. When given in effective doses to intact rats, indomethacin, unlike anti-inflammatory steroids, did not affect the size of the adrenals or thymus, or retard gain in body weight. Its anti-inflammatory activity does not depend upon activation of the adrenals, since it was fully active in adrenalectomized rats.

The anti-inflammatory activity of INDOCIN was also demonstrated by its ability to inhibit edema formation induced by subplantar injection of carrageenin in rats. By this test, the relative potency of indomethacin was: 30 times aspirin, 20 times phenylbutazone, and 2 times hydrocortisone. INDOCIN does not possess antihistaminic or antisertonin activity, since it did not affect edema induced by injection of egg white, serotonin, or yeast. Combinations of indomethacin and a steroid were more effective than comparable doses of either drug alone in inhibiting granuloma growth or edema formation.

#### Antipyretic Activity

INDOCIN is an antipyretic in laboratory animals. In rabbits it was about 20 times as potent as phenylbutazone and 10 times as potent as aminopyrine. Its duration of action was much longer than that of aminopyrine and comparable to that of phenylbutazone. In rats indomethacin appeared to be about 10 times as potent as phenylbutazone.

The antipyretic activity of INDOCIN has been confirmed clinically by observations in patients with Hodgkin's disease, acute rheumatic fever, and a variety of other acute febrile conditions.

#### Analgesic Activity

Laboratory tests designed to detect mild analgesic activity indicate that indomethacin is more potent than aspirin or aminopyrine.

INDOCIN®  
(Indomethacin)

Ph. 262301

*Absorption and Excretion*

INDOCIN is well absorbed after oral administration in all animals, including man. In dogs, monkeys, rats, and man, peak plasma levels after an oral dose occur within 0.5 to 2 hours. The drug present in the plasma of dog and man is virtually all unchanged indomethacin, but a metabolite (probably the glucuronide conjugate) may be present for the first half hour after intravenous injection in the guinea pig.

The route of excretion is related to the species of animal and is independent of the route of administration or size of dose. Nearly all the compound could be recovered in urine and feces. The rabbit eliminates indomethacin almost entirely in the urine, while the dog excretes nearly all the compound in the feces. The rat, guinea pig, monkey, and man eliminate it by both routes. In man, about two-thirds of the drug is excreted in the urine.

In rabbits, rats, guinea pigs, and monkeys, some indomethacin is metabolized by deacetylation or demethylation and the metabolites are excreted in the urine as such or as the glucuronide conjugate. In man, however, no evidence of molecular breakdown has been observed, and virtually all of the material excreted in the urine is indomethacin glucuronide.

**AVAILABILITY**

No. 3316—INDOCIN capsules, 25 mg. each, are opaque blue and white, imprinted with an MSD trademark and potency, and are supplied in bottles of 100.

No. 3317—INDOCIN capsules, 50 mg. each, are opaque blue and white, imprinted with an MSD trademark and potency, and are supplied in bottles of 100.

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**Merck Sharp & Dohme**  
Division of Merck & Co., Inc.

West Point, Pa.

Effective May 1965

Printed in U.S.A.

**Dr. McCLEERY.** The approved package labeling—package insert—includes the allowable claims and the required precautionary and warning information which is to be included in advertisements and promotional labeling of a prescription drug like Indocin.

As you will see, the Indocin package insert limits the use of this drug to four indications: (a) rheumatoid arthritis, (b) rheumatoid (ankylosing) spondylitis, (c) degenerative joint disease (osteoarthritis) of the hip, and (d) gout. This labeling indicates that Indocin will relieve pain, reduce fever, swelling and tenderness, and increase mobility in patients with rheumatic disorders. Indocin is a potent drug and, as the package insert shows, it has many side effects, contraindications, precautions, and warnings that must be heeded for its safe and effective use. For these, and other, reasons, it was not approved for use in all rheumatic disorders, but only for those rheumatic disorders I have named.

The Indocin Bulletin No. 83, dated July 12, 1965, is typical of the group of instructions sent out during that time period. So that your committee may consider the bulletins as a group, I am including copies of the group as exhibit B for the record. These were sent out to Merck detail men.

**Senator NELSON.** They will be printed in the record at this point.  
(The information referred to follows:)

#### BULLETIN NO. 83, JULY 12, 1965

To : All Associates Western District.

From : H. Glassner.

Subject : 'Indocin.'

One of the reasons a real Senior Salesman like John Brekke consistently writes over \$300,000 a year is that the physicians in his territory believe him.

Physicians believe John because he tells them a concise, clear story that meets their needs, their wants, their desires, or allays their anxieties. Here is John Brekke's story on 'Indocin'. I'll bet he leads them with this.

"Doctor, I'm certain that in your busy practice no day passes without several patients seeking your help from the misery inflicted by painful, reddened, swollen, feverish joints—the classic signs of inflammation.

It is true that short term therapy with 'Decadron' has offered dramatic relief to many of these patients.

However, today, with 'Indocin', a new compound which is not a steroid—you can offer these patients new hope, new vistas of relief from their pain and an extended margin of safety.

More than 300 clinicians both here and abroad have concluded that when there is heat—redness—swelling—and pain in the muscle or joints—'Indocin' is usually effective.

'Indocin' is indomethacin—a modification of the naturally occurring amino acid tryptophan. 'Indocin' is chemically unique. 'Indocin' is not an aminopyrine derivative like phenylbutazone nor is 'Indocin' a steroid.

'Indocin' relieves stiffness, reduces swelling, alleviates tenderness, decreases fever, and above all soothes pain.

The advantages of 'Indocin' are these:

1. Therapy with 'Indocin' is safer. Clinical investigation in thousands of advanced cases has shown 'Indocin' to have a remarkable record of safety.

2. Therapy with 'Indocin' is rapid in onset of action. In many cases—particularly in acute flare ups of gouty arthritis—relief of pain is evident in 2-4 hours.

3. Usually on therapy with 'Indocin' tenderness and heat subside in 24-48 hours and swelling is reduced in 3-10 days depending upon the severity of the condition being treated.

4. Furthermore, unlike steroids, tolerance to 'Indocin' has not been reported.

4. The dosage schedule with 'Indocin' is simple and uncomplicated. Usual-

ly 1-25mg capsule of 'Indocin' 2-3 times a day taken with meals—does the job.

If necessary 1 capsule per day may be added at weekly intervals up to a maximum dose of 8 capsules per day.

In acute gout, where speed of relief is urgent, 2 capsules of 'Indocin' t.i.d. may be given until the flare up is controlled.

5. Unlike toxic aminopyrine derivatives or steroids, the side effects of therapy with 'Indocin' are usually minor and seldom constitute a problem. Usually they can be controlled by simple adjustment of dosage.

Like all new agents today therapy with 'Indocin' is contraindicated in pregnancy. Other than that the only contraindications to therapy with 'Indocin' are ulcerative colitis, active peptic ulcer and gastritis. These are not unusual since as you know doctor, even aspirin causes some gastric complaints.

The other side effects are not serious. Some patients on therapy with 'Indocin' may experience headache, dizziness, or lightheadedness, and even some minor G.I. disturbances. This effect can be minimized by giving 'Indocin' with meals. Headaches usually disappear after the patient has had a cup of coffee.

Doctor, clearly 'Indocin' represents a giant step forward in the safe and effective treatment of the misery inflicted by arthritic diseases. I'm certain you have in your practice ten or more patients who right now—today—would welcome the dramatic relief 'Indocin' can afford.

Would you like some starter doses of 'Indocine' for those patients whom you want to start on 'Indocin' therapy today? 'Indocin' is now stocked at the pharmacies in this area. You may prefer to call your prescriptions in right now rather than bother or have the patient come in."

There's a detail that clearly should convince the physician that

Whenever the problem is oppressive joint pain associated with heat, redness, tenderness and swelling.

When the muscles around an inflamed joint are in spasm causing a limitation in motion.

Whether the tentative diagnosis is osteoarthritis of the hip, gout, rheumatoid arthritis, rheumatoid spondylitis, or just plain muscoskeletal aches and stiffness.

For short term use in acute conditions or long term use in chronic diseases.

'Indocin' will afford relief to three out of four patients effectively—with an extended margin of safety—with fewer tablets—at less cost—with less dosage adjustment—and therefore fewer problems for both the physician and his patient than any other currently available product.

Unless you've got a better story put together I would suggest you consider using this one. It will sell 'Indocin'.

#### BULLETIN No. 84, JULY 14, 1965

To : All Sales Associates in the Western District.

From : H. Glassner.

Subject : 'Indocin.'

Top salesmen reach peak sales ability by training their instincts to think of advantages and benefits. Such men react naturally, instantaneously, and instinctively with maximum selling power to the physicians needs, desires, wants, or fears. Some trainers call this the "hot button approach".

You call on a busy physician. He is thinking about his patients' problems. Only when you give him a glimpse of some advantage he does not now enjoy will he listen.

Charlie Mitchell has done just that with his approach on 'Indocin'. With many years of experience on a regular territory and now with over eighteen months of experience in a specialist-hospital territory Charlie has learned the need for personalizing each presentation. Here are three attention getting hot button individualized approaches he is planning to use.

For the G.P.

Doctor, you do agree that in the treatment of chronic rheumatoid diseases—aspirin is too weak for optimal effect.

You no doubt also will agree that the aminopyrine derivatives such as Butazolidin and the steroids like Prednisone are too risky for long term use.

Yet, until now, aspirin, aminopyrine derivatives, and steroids have been the only major agents available for relieving pain and reducing disability in a whole host of rheumatic problems.

Now, today, 'Indocin'—a new non-steroidal anti-inflammatory agent which approaches the potency of the steroids>equals or surpasses the effectiveness of Butazolidin—but which in therapeutic doses has a safety index comparable to aspirin is

Available to relieve pain.

Reduce fever tendencies and swelling and increase joint mobility in patients with rheumatic disorders.

For the physician who is presently prescribing Darvon.

Doctor, you no doubt agree that pain and disability are the most common complaints of patients with rheumatoid problems.

Would not a drug that can control long term pain in such patients yet in therapeutic doses be as safe as aspirin fill a real need?

'Indocin'—a new non-steroidal anti-inflammatory agent has a potency equal to or greater than Butazolidin—which as you know is an aminopyrine-like synthetic.

'Indocin' usually controls acute arthritic pain within one to two hours.

However, 'Indocin' is more than just an ordinary analgesic like aspirin or Darvon because 'Indocin' has anti-inflammatory activity which is almost equal to full dose steroids.

For the conservative therapeutic nihilist.

Doctor, it is true that no patient ever dies from chronic rheumatoid arthritis—but they do become cripples who live a very limited life.

The burden of crippling disability imposed by chronic rheumatoid arthritis can now be lifted in three out of four patients on therapy with 'Indocin'.

No matter what approach you use—no matter what story you tell—make certain that when you leave the office the physician agrees that

Whenever the problem is oppressive joint pain associated with heat, redness, tenderness, and swelling—

When the muscles around an inflamed joint are in spasm causing a limitation in motion—

Whether the tentative diagnosis is osteoarthritis of the hip, gout, rheumatoid arthritis, rheumatoid spondylitis, or just plain muscoskeletal aches and stiffness—

For short term use in acute conditions or long term use in chronic diseases—

'Indocin' will afford relief to three out of four patients effectively—with an extended margin of safety—with fewer tablets—at less cost—with less dosage adjustment—and therefore fewer problems for both the physician and his patient than any other currently available product.

Go get it!!!

#### BULLETIN No. 87, JULY 20, 1965

To : Mr. Gordon R. Klodt.

From : H. Glassner.

Subject : 'Indocin' Profit Plan Objectives.

Surely you jest. The 'Indocin' Profit Plan Objectives for the Western District have just arrived. Your ouija board has a definite short circuit. The figures you forwarded are so ridiculously low that they are a rank insult to the hottest, sellingest district in the country. Only because these figures will appear on the official R-300 and R-317 reports beginning with July, 1965 are we even bothering to forward them to our associates since we intend to smash them.

We realize these dollar objectives were calculated by determining the percentage of sales in each territory of 'Decadron' Tablets and Injection, 'Decagesic', 'Benemid' and 'ColBenemid'. Apparently, the same percentages were then used in determining the percentages of the total objective for each territory on 'Indocin'. Apparently, you next built the territory objectives into the Field Manager Group objective and then the district total. Yet even though your approach

was rational, I'll Bet You the Price of a Bottle of Your Favorite Booze that the Western District Beats this Objective by at Least 50% This Year.

Heck, Gordon, 'Indocin' is the hottest product we've had come down the pike in many a moon. Our guys are primed at fever pitch. Competition is running scared. Results on recalls look great.

The only questions we are getting regularly are easily handled such as:

Does 'Indocin' affect prothrombin levels? The answer, of course, is "No."

Does 'Indocin' affect glucose tolerance? The answer, again, of course is "No." 'Indocin' can be safely used on the diabetic patient.

In fact, our guys are using a real expanded claim for 'Indocin' on inflammation. They are consistently telling their doctors that—

Whenever the problem is oppressive joint pain associated with heat, redness, tenderness, and swelling—

When the muscles around an inflamed joint are in spasm causing a limitation in motion—

Whether the tentative diagnosis is osteoarthritis of the hip, gout, rheumatoid arthritis, rheumatoid spondylitis, or just plain musculoskeletal aches and stiffness—

For short-term use in acute conditions, or long-term use in chronic conditions—

'Indocin' will afford relief to 3 out of 4 patients effectively—

With an extended margin of safety—

Probably with fewer tablets—

Therefore, at less cost—

With less dosage adjustment—

And, therefore, fewer problems for both the physician and his patient than any other currently available product.

For these reasons—we intend to really roll up the 'Indocin' bonus credit points this year. We'll be laughing at you when we make our year's objective by October 30.

#### BULLETIN No. 88, JULY 21, 1965

To : All Western District Sales Associates.

From : H. Glassner.

Subject : 'Indocin.'

Jim Blake is kind of new. He is a pharmacist, so he has developed a very healthy respect for what drugs will and won't do. I suppose he just doesn't know any better than to sit down and prepare a detail that puts side effects in their proper perspective. Here is how he is handling the side effects on 'Indocin'.

"Chemically, 'Indocin' is indomethacin. The only similarity in structure between 'Indocin' and steroids or phenylbutazones is that all three are organic compounds. After that, the similarity ceases.

The ability of both the steroids and phenylbutazones to relieve inflammation is unquestionable. However, both of these agents cause undesirable—and, in the case of phenylbutazones—even hazardous side effects. So, doctor let's examine the relative lack of side effects of 'Indocin'.

In six out of ten patients on 'Indocin', you need anticipate no adverse effects whatsoever.

In two out of three of these ten patients, some bothersome effects might occur. Bothersome is probably as severe an adjective as we can use to describe these effects because in most patients they are tolerable, and transient.

Reports of changes in the white blood count of patients on therapy with 'Indocin' have been extremely rare. In most cases, it has been impossible to implicate 'Indocin' as the causative agent. Unlike phenylbutazone, patients on therapy with 'Indocin' do not require weekly or bi-weekly blood counts.

Unlike steroids, therapy with 'Indocin' does not depress adrenal function, decrease resistance to infections, or present withdrawal problems.

The percentage of patients experiencing side effects, which are listed in this chart, needs some explanation. Originally, our studies on 'Indocin' were done with tablets. For some unknown reason, the tablets did not disintegrate properly and absorption was erratic. Now, commercially, 'Indocin' is being marketed as a capsule. In capsule form, 'Indocin' has not caused as high a percentage of even these minor reactions. These charts, however, do include the side effects experienced with the earlier tablets which are not even available on the market. Therefore, the incidence of adverse reactions which you

probably will experience in your patients will be somewhat lower than these figures indicated here.

You will note that gastrointestinal disorders head the list. This irritating effect can be markedly reduced by taking 'Indocin' after meals.

Headaches are next in frequency. These headaches are mild and are readily relieved by caffeine. Usually a cup of coffee does the job.

Lightheadedness and dizziness occurs occasionally with 'Indocin' as with almost any other medication. For the most part, these effects are very mild and very transient.

Diarrhea accounts for less than 2% of all reactions.

You will also note that the incidence of peptic ulcer is less than 1.5%. Since it is estimated that 7 to 7.5% of all arthritic patients have ulcers—Probably Because of the Large Amounts of Aspirin and Steroid Which These Patients Have To Take Over Long Periods of Time—It is hard to construe this effect of 'indocin' as being a true side effect.

In summary, doctor, six out of ten patients on 'Indocin' probably will experience no adverse reaction.

Two out of three of these ten patients may experience some mild adverse effects which are transient and tolerable.

And, only one out of ten of these patients will probably experience side effects severe enough to warrant a reduction of dosage.

On the basis of these complete figures—you will agree that 'Indocin' does Extend All the Margin of Safety—in the management of arthritic disorders."

With a complete and candid explanation on side effects such as this, it is difficult to see how any physician can refuse to believe that Whenever the Problem Is Oppressive Joint Pain Associated With Heat, Redness, Tenderness, and Swelling—

When the Muscles Around an Inflamed Joint Are in Spasm Causing a Limitation in Motion—

Whether the Tentative Diagnosis Is Osteoarthritis of the Hip, Gout, Rheumatoid Arthritis, Rheumatoid Spondylitis, or Just Plain Musculoskeletal Aches and Stiffness—

For Short-Term Use in Acute Conditions or Long-Term Use in Chronic Conditions—

'Indocin' Will Afford Relief to Three Out of Four Patients Effectively—With an Extended Margin of Safety—

Probably With Fewer Tablets—

and, Therefore, Less Cost—

With Less Dosage Adjustment—

and, Therefore, Fewer Problems for Both the Physician and the Patient Than Any Other Currently Available Product.

Tell 'Em Again, and Again, and Again.

Tell 'Em Until They Are Sold and Stay Sold!

#### BULLETIN No. 93, JULY 28, 1965

To: All Western District Sales Associates.

From: H. Glassner.

Subject: Profit Improvement Promotional Program 'Indocin', August, 1965.

All reports indicate that this one is a Real Winner. Our dollar volume on 'Indocin' in June was basically the automatic shipments. Therefore, these figures are of limited value in assessing individual sales performance as regards repeat orders. Instead, please rely on the weekly tabulations in Angel Town Topics to measure your rate of progress on 'Indocin'. Pick up ten or fifteen new prescribers each week on 'Indocin' and you'll move to the top of your group.

Obviously, 'Indocin' sales greatly Exceed all initial sales forecasts. New revised projections are being developed at West Point. These will be more in line with actual sales experience. Sometime prior to the end of August, your revised 1965 objective on 'Indocin' will be forwarded to you. My guess is that our original objective will be tripled. Mr. Klodt just hates to lose any bet. The best way to beat this—or any other objective—is to continue to sell II—out of 'Indocin'.

It is imperative to do this because time is going to run out. One and probably two additional red-hot items are scheduled for release by October 1. Obviously, these new products will also require and get our all-out effort at the time of

their release. In addition, it is reported in trade journals that both Upjohn and Parke Davis are reaching the final stages of research on anti-inflammatory products of their own. Those, as I understand it, are nonsteroidal.

Obviously, this leaves no time to procrastinate on 'Indocin'. We must establish 'Indocin' firmly during the next sixty days—or it will be too late!

In August, here's what we have to work with:

	R.D. value
150 'Indocin' 25 mg.—21's (3150 tablets)-----	\$225
50 'Indocin' 25 mg. (3 x 6) (900 tablets)-----	63
150 'Indocin' Detail Folders-----	35
150 'Indocin' Folder-Index Cards-----	15
150 'Indocin' Dosage Cards-----	9

Add to this figure the cost of having you make 139 to 140 presentations on 'Indocin' this month, plus the cost of journal ads and direct mail necessary to support your efforts in your territory. Then, as a businessman—ask yourself how many dollars in 'Indocin' sales You need to get back to make enough profit to plow \$32.0 million in to Research to give You new products.

Before you make any call on 'Indocin' in August, ask yourself these questions:

1. Why am I calling on this physician?
2. What is he presently using in lieu of 'Indocin'?
3. What hits his "hot button" . . . fear, effectiveness, safety, price, etc.
4. Just what am I going to tell him today that will make it imperative for him to Prescribe 'Indocin' Today?

After you have made that call, ask yourself just one question to measure your own effectiveness:

1. Based on what I just did in that office . . . How many tablets of 'Indocin' is that physician likely to prescribe this month?

Let's face it! 'Indocin' is a superior therapeutic agent. The documented F&DA approved claims indicate that 'Indocin' relieves the pain, reduces the stiffness, tenderness, and fever—and increase joint mobility in patients treated with 'Indocin' when the diagnosis has been acute and chronic rheumatoid arthritis, osteoarthritis of the hip, ankylosing spondylitis, and acute and chronic gout. These clinical entities are the toughest, most resistant, most prolonged rheumatic lesions the specialist is likely to encounter.

Since 'Indocin' is known to convey effective relief from the pain and inflammation of these most difficult lesions and to do this with an extended margin of safety, it is obvious that 'Indocin' will work in that whole host of rheumatic crocks and cruds which every General Practitioner, Internist, and Orthopedic Surgeon sees everyday in his practice. For these entities he is presently prescribing steroids, aminopyrine-like butasones, aspirin, or limited analgesics like Darvon and the almost worthless muscle relaxants.

Remember, until 'Indocin,' the physician who wished to use medication had only four classes of drugs available to him:

1. Aspirin or simple aspirin-like analgesics which only relieve pain.
2. Steroids which only relieve inflammation.
3. Butasolidin or other aminopyrine derivatives which are too dangerous for prolonged use.
4. Muscle relaxants which rarely work and, at best, only temporarily relieve.

Today, 'Indocin' effectively does all of these things with just one tablet. 'Indocin' is anti-inflammatory. 'Indocin' is analgesic. 'Indocin' breaks up the pain—spasm—pain cycle, thus increasing joint mobility. Yet, 'Indocin' is neither a steroid nor an aminopyrine derivative—but, rather, a unique, new chemical entity which affords an extended margin of safety in the long-term management of arthritic disorders.

Run scared! Get a sense of urgency into every presentation. When you do, you will convince the physician that—

Whenever the problem is oppressive joint pain associated with heat, redness, tenderness, and swelling. . . .

When the muscles around an inflamed joint are in spasm causing a limitation in motion. . . .

Whether the tentative diagnosis is osteoarthritis of the hip, gout, rheumatoid arthritis, rheumatoid spondylitis, or just plain musculoskeletal aches and stiffness. . . .

For short-term use in acute conditions or long-term use in chronic conditions. . . .

'Indocin' will afford relief to 3 out of 4 patients effectively. . . .

With an extended margin of safety . . . probably with fewer tablets . . . and, therefore, at less cost . . . with less dosage adjustment . . . and, therefore, fewer problems for both the physician and the patient than any other currently available product.

You've told this story now, probably 130 times. The physician, however, has heard it only once. So, go back and tell it again and again and again until it is indelibly impressed in his mind and he starts—and continues—to prescribe 'Indocin.'

Let's go!

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BULLETIN No. 95, AUGUST 4, 1965

To: All Western District Sales Associates.

From: H. Glassner.

Subject: Profit Improvement Promotional Program—"Indocin."

Bill Benedict brought back from the meeting in Chicago a group of the most common questions you have been asked about 'Indocin.' Unfortunately, we do not have all of the answers. As you get questions—shoot them in and we'll try our best to get you an answer you can use.

1. What is the mode of action of 'Indocin'? Where does it work?

'Indocin' exerts its anti-inflammatory—analgesic and antipyretic effects at the tissue level. How it works is not yet clear since chemically Indomethacin represents the first of a whole new group of compounds.

2. How can an analgesic cause headache?

This phenomenon also is not yet clear. The direct central action of 'Indocin' is very slight. It is presently postulated that 'Indocin' may exert some peripheral vaso dilatory effect . . . which causes a mild headache-type central reflex.

3. Will 'Indocin' work in any musculoskeletal inflammatory reaction?

Yes. However, in submitting the original claims for an approved N.D.A. . . . it was obviously important to demonstrate both the effectiveness and safety of 'Indocin' in the toughest and most resistant cases. These are the only cases that top-notch investigators will follow. 'Indocin' works effectively in those resistant cases. Other specific claims, such as bursitis, fibrositis, etc., will be forthcoming. 'Indocin' works in these entities. From the point of view, of daily clinical practice, the physician himself will expand the uses to suit his practice. 'Indocin,' however, is a broad-spectrum anti-inflammatory agent which is specific for inflammatory lesions of the musculoskeletal system.

4. Is 'Indocin' indicated for bronchial asthma?

No. Bronchial asthma is an acute or chronic allergic disease. While there is lots of inflammation present . . . it takes a specific anti-allergic agent such as 'Periactin' or 'Decadron' to work effectively in bronchial asthma.

5. Why is the maximum dose of 'Indocin' only 200 mg./day?

That is all it takes to get the job done. Going beyond that limit does not appreciably increase the effectiveness of 'Indocin' and does seem to increase the severity of the side effects one may anticipate.

6. Does 'Indocin' alter the pH of body fluids or urine?

No. 'Indocin' has no affect on the pH of blood or urine.

7. Can 'Indocin' be safely administered to a diabetic?

Yes. 'Indocin' has no effect on glucose, metabolism or glucose tolerance in either the normal patient or a diabetic patient.

8. Can 'Indocin' be safely administered to a patient who is taking anticoagulants? Does it affect prothrombin time?

'Indocin' has no affect on prothrombin time. 'Indocin' can be safely administered to a patient who is also taking anticoagulants.

9. Will antiacids interfere with absorption of 'Indocin' from the G.I. tract?

No. Antiacids may be administered concomitantly with 'Indocin.'

10. When will reprints on 'Indocin' be available?

As soon as the papers are published in journals of wide circulation . . . probably within the next three to six months.

It is becoming evident that the greatest mistake we can make with 'Indocin' is NOT to remind the physician that--

Whenever the Problem is Oppressive Joint Pain Associated With Heat, Redness, Tenderness, and Swelling. . .

When the Muscles Around an Inflamed Joint Are in Spasm Causing Limitation of Motion. . .

Whether the Tentative Diagnosis is osteoarthritis of the Hip, Gout, Rheumatoid Arthritis, Rheumatoid, Spondylitis, or Just Plain Musculoskeletal Aches and Stiffness. . .

For Short-Term Use in Acute Conditions or Long-Term Use in Chronic Conditions.

'Indocin' Will Afford Relief to 3 Out of 4 Patriots Effectively. . . .

With an Extended Margin of Safety. . . .

Probably With Fewer Capsules. . . .

And, Therefore, Less Cost. . . .

With Less Dosage Adjustment. . . .

And, Therefore, Fewer Problems for Both the Physician and the Patient Than Any Other Currently Available Product.

This Is a Big One. Keep Sellin' It !

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#### BULLETIN No. 23, APRIL 5, 1967

To : All sales Associates.

From : H. Glassner.

Subject : Profit Improvement Promotional Program Indocin-April Promotion.

During 1966, the Western Region with 10.8% of the nation's manpower, contributed 10.3% of the nation's total volume on Indocin.

That was not very good.

Now for the first two months of 1967, we have contributed only 10.1% of the nation's total volume on Indocin.

That is even worse.

While for two months of 1967, the nation had a 32.6% increase in Indocin sales, the Western Region had only a 25.0% increase.

For the two month period we are 0.6% behind our Profit Plan Objective on Indocin.

District rankings, giving equal weight to percent of objective attained and percentage increase over 1966 sales follow. Remember 66.6% of objective is par.

District	Total sales	Percent of quantity of objective attained	Percent plus/minus 2 months of 1966
Perttula's Pirates.....	\$105,285	72.7	35.3
Westmoreland's Wranglers.....	71,999	73.3	31.2
Benedict's Bombers.....	92,875	67.8	31.3
Waddle's Warriors.....	124,867	69.2	21.6
Feudin Hatfields.....	63,151	60.6	24.6
McCabe's Maulers.....	70,224	60.8	20.9
Lundahl's Lumberjacks.....	89,892	56.8	12.0
Region.....		66.0	25.0
Nation.....			32.6

Top three and low three volumes among our regular representatives for the two month period were turned in by :

1. Joe Powell, \$18218.
2. Rich Mazziotti, \$16331.
3. Bud Iversen, \$13002.
68. Roger, Hillman, \$4406.
69. Dan Taylor, \$3225.
70. Fred Mansho, \$3027.

Tabulations of two month sales on Indocin, ranked by the percentage of objective attained, for all regular territories is attached.

#### The Tools

During April you will be working with the following assortment :

75 Indocin 25mg (3x6)---1350 Capsules-----	\$98
25 Indocin 25mg---21's---525 Casules-----	37
50 Indocin Folder Index Cards 296L-----	5
Total -----	140

So far in 1967, Joe Powell has gotten almost a 70 fold return on his monthly Indocin promotional assortment.

What is your return on the investment of promotional material which you have made?

#### *The Plan*

Our objective in April and every month in 1967 is to narrow the gap between your sales and the top sales in the Region.

This can best be done by "Selective Detailing"—bringing the right product to the right physician with the right theme. The theme must be one that allays his fears, or makes his therapy more effective, safer, or more economical.

Indocin is an easy product to be selective about. Sales and Marketing Research studies show that general practitioners and internists prescribe more than 90% of all the nonsteroidal anti-inflammatory, anti-arthritis agents used. Therefore, in April . . . pin point your shots. Select no more than 30 general practitioners and/or internists for a hard hitting detail on Indocin.

Let's be realistic. By this time most physicians have seen, read, or heard about the report in the New England Journal of Medicine and/or the Wall Street Journal.

The general practitioner and internist in private practice is a mature, pragmatic individual. He realizes that his patients can not afford the luxury of "Ivory Tower" thinking.

The arthritic he sees in his daily office practice demands prompt relief of pain.

The arthritic he sees in daily office practice demands an anti-inflammatory agent that will relieve swelling and increase joint mobility so that he can become productive.

The private practitioner realizes that the arthritic he sees in daily practice will probably be taking medication on a chronic basis. He wants a preparation that can be taken for the long term with as few hazardous side effects as possible.

Indocin is an effective anti-inflammatory agent that is suitable for long term as well as short term use in adult patients who are not pregnant.

Indocin has been found effective in relieving pain; reducing fever, swelling, and tenderness; and increasing mobility in patients with rheumatoid arthritis, rheumatoid spondylitis; osteo arthritis of the hip and gout.

Indocin is much more than a simple analgesic. It is a unique chemical entity unrelated to aspirin, steroids, colchicine or phenylbutozine.

Let's stand on our little old two feet this month and sell the benefits of Indocin.

When some hard-nosed physician brings up one of the recent "controlled" studies reported in the Wall Street Journal . . . Rich Mazziotti stops him cold by opening the Indocin literature to the bibliography and simply asking . . .

"Doctor, can all of these physicians of impeccable reputation really be wrong?"

"Doctor, can your own experience with Indocin in your own practice these past 33 months really be wrong?"

Take off the kid gloves. If he wants to use aspirin as base line therapy, let him use it. Chances are the patient is already taking aspirin. He has come to the physician because aspirin alone is not affording satisfactory, optimal effects.

When aspirin alone is not enough . . . Indocin is the logical prescription of choice.

District Managers report that because Edecrin was on primary promotion in March, most of you still have a supply of the leave detail piece sent for use in March. It is a good one. Use it in April to show general practitioners how to maximize the benefits of Indocin for their patients. If you do this effectively, your pockets can swell with extra bonus bucks.

Let's go back down to selling Indocin again.

## INDOCIN, JANUARY THROUGH FEBRUARY 1967

	Volume	Percent		Volume	Percent			
<b>Group:</b>								
Lachman	\$7,887	79	Benedict's group—Continued					
Lockett	9,235	73	Richardson	\$6,908	64			
Putnam	8,450	70	Blake	8,870	64			
Lewine	8,100	70	Filler	8,584	64			
Tonkyro	8,633	67	Total	92,876	68			
Groos	10,475	60						
Total	71,999	73	<b>Lundahl's group:</b>					
<b>Perttula's group:</b>								
Mazzotti	16,331	91	Walker	7,892	64			
Woolley	11,160	83	Collins	6,110	64			
Houts	10,101	71	Knight	6,835	63			
Number 2626	8,456	71	Doody	7,510	62			
Wolfe	7,136	70	Nolan	5,796	60			
Washington	5,662	69	Locke	9,018	58			
Mustard	6,017	69	Hydeman	9,392	58			
Mickelson	7,930	66	Harris	5,817	54			
Edwards	9,638	66	Peper	9,061	52			
Hammang	8,311	66	Stewart	8,579	52			
Brekke	11,914	62	Lanciotti	5,006	51			
Total	105,285	73	Wessells	7,879	50			
			Total	89,893	57			
<b>Waddle's group:</b>								
Powell	18,218	83	<b>McCabe's group:</b>					
Iverson	13,002	77	Mele	7,335	74			
Bentley	10,118	71	Gray	12,851	66			
Smith	10,482	69	Chalmers	7,984	66			
Pies	10,890	62	Ayala	7,365	61			
Hart	7,053	65	Chazankin	4,985	61			
Cargile	8,144	64	Callan	9,184	60			
Ginger	11,588	63	Kearney	5,557	57			
Hilliker	12,045	62	Hillman	4,406	53			
Yarborough	8,632	61	No. 2720	6,197	51			
Kohls	8,199	58	Total	70,225	61			
Total	124,868	69	<b>Hatfield's group:</b>					
<b>Benedict's group:</b>								
Brown	8,846	77	Furr	4,456	65			
Nordquist	5,109	72	O'Brien	8,456	64			
Alfano	9,282	70	Burgess	7,052	63			
DuBois	9,469	69	Allen	8,600	63			
Solari	7,182	68	Pederson	5,910	60			
Lazarus	4,159	68	Mansho	3,027	59			
Lawing	9,052	67	Koberstein	9,446	57			
Vitt	7,846	65	Baker	4,196	52			
Strinz	6,315	66	Taylor	3,225	62			
			Total	63,151	61			
			Region total	618,955	66			

## BULLETIN No. 66, JULY 17, 1967

To: All Western Region Sales Associates.

From: H. Glassner

Subject: Profit-Improvement Promotional Program, 'Indocin'.

## PAST PERFORMANCE

For five months of 1966, with 10.8% of the national manpower, the Western Region has contributed 10.7% of national sales on 'Indocin'.

While the nation was 22.6% ahead of the same period in 1966, this region was 24.7% ahead.

At the end of five months, we were running about 2.5% ahead of our Profit Plan for 'Indocin'.

These figures, of course, include the orders that were dated in April and May. However, package sales for June indicate we are again increasing sales of 'Indocin'. It appears the bad publicity we had early in the second quarter is now behind us.

The standings, by district, for five months follow:

District	Amount	Percent of objective attained	Percent, plus/minus 1966
1. Westmoreland's Wranglers.....	\$187,687	95	36.9
2. Perttula's Pirates.....	274,432	93	30.8
3. Benedict's Bombers.....	253,019	91	30.1
4. Waddle's Warriors.....	334,788	91	26.8
5. Feudin' Hatfields.....	173,145	81	25.1
6. McCabe's Maulers.....	182,489	77	15.0
7. Lundahl's Lumberjacks.....	240,614	74	10.3
Region.....		86	24.7
Nation.....			22.6

Top three sales volumes in the region for five months on 'Indocin' were turned in by:

1. Joe Powell, \$46,024.
2. Rich Mazziotti, \$36,560.
3. Dean Hilliker, \$35,884.

#### THE TOOLS

During the months of July and August, you will be working with the following assortment:

125 'Indocin' 25 mg. (3 × 66)—2250 capsules.....	\$140
50 'Indocin' 25 mg.-21's—1050 capsules.....	70
50 'Indocin' Folder-Index Cards, 530L.....	10
2 'Indocin' Permanent Detail Piece, 612L.....	20
250 'Indocin' Telephone Pads.....	30
50 'Indocin' "How to Use Leaflets?".....	10
<b>Total</b> .....	<b>280</b>

Joe Powell is making an average monthly assortment return \$60 for every \$1 he expands in promotional material.

What is your batting average?

#### THE PLAN

A recent report from Sales & Marketing Research on the reputation and usage of various drugs in severe rheumatoid arthritis points the way to increased opportunities.

In this study, physicians identified any patient with severe rheumatoid arthritis as one afflicted with pain and crippling so severe he could not perform his usual activities, often needed to be cared for by others, and had objective evidence of severe disease. The survey found the following attitudes among general practitioners and internists relative to severe rheumatoid arthritis:

1. 'Indocin' held only 19% of the severe rheumatoid arthritic market.
2. 'Indocin' was the second most often prescribed product in this market.
3. Eight out of ten physicians questioned, sometimes use 'Indocin' in the treatment of severe rheumatoid arthritis, yet seldom used it as the first drug they prescribed.
4. Almost five out of ten physicians questioned do not use 'Indocin' as either the first or the second drug to treat severe rheumatoid arthritis.
5. Two other products, aspirin and Darvon, have 48% of the severe rheumatoid arthritic market.
6. Eighteen per cent of the physicians questioned treated all of their severe rheumatoid arthritic patients with aspirin. Yet, G.I. side effects were considered as a bad characteristic of aspirin more frequently than of 'Indocin'.
7. Only aspirin had a better reputation for efficacy and few side effects than did 'Indocin'. Darvon has a more favorable reputation for fewer side effects but a less favorable reputation for efficacy than does 'Indocin'.
8. Butazones, corticoids, and gold salts, hold 33% of the severe rheumatoid arthritic market. Yet, these more potent products have a less favorable reputation among physicians using them for efficacy and side effects than does 'Indocin'.

Obviously, we have done a good job of selling 'Indocin' for long-term management of chronic rheumatoid arthritis. Now, we must convince our physicians to use 'Indocin' for short, severe, flare-ups.

There is room for continued growth of 'Indocin' in the treatment of severe rheumatoid arthritis—where pain and crippling are so severe that the patient cannot function normally. This growth can come from two areas:

1. From the many physicians who prescribe therapy which is "more potent" than therapy with 'Indocin' (i.e. butazones, steroids, and gold) before trying 'Indocin', and

2. From those severely afflicted patients who are not adequately controlled by aspirin or Darvon, i.e. when pain-killers no longer give adequate control or when they only kill pain without reducing inflammation or improving joint mobility. . . . 'Indocin' should be tried promptly or even tried first.

Remember, and make sure your physicians realize that 'Indocin' is an effective anti-inflammatory agent that is suitable for short-term as well as long-term use in adult patients.

Remember, and make sure your physicians realize that unlike aspirin and Darvon 'Indocin' has been found effective in not only relieving pain but reducing fever swelling, and tenderness . . . and increasing joint mobility in the symptomatic treatment of rheumatoid arthritis.

Remember, also, and be sure your physicians realize that for patients with acute, severe rheumatoid arthritis, or acute flares of chronic rheumatoid arthritis, the total daily dose of 'Indocin' may be increased by one capsule per day until a satisfactory response is obtained or a total daily dose of six to eight capsules a day is reached.

We have not really scratched the surface on this one yet.

Let's start digging this month.

#### INDOCIN, JANUARY THROUGH MAY 1967

	Volume	Percent		Volume	Percent
Westmoreland's group:			Benedict's group—Continued		
Lachman.....	\$19,936	98	Vitt.....	19,958	83
Putnam.....	23,413	95	Lazarus.....	10,325	83
Lockett.....	24,007	92	Group.....	253,019	91
Tonkyro.....	24,020	91	Lundahl's group:		
Lewine.....	21,053	89	Collins.....	18,943	98
Adams.....	27,512	78	Walker.....	22,593	90
Group.....	189,687	95	Locke.....	25,379	81
Pertulla's group:			Doody.....	20,018	81
Mazzotti.....	36,560	100	Hydeman.....	24,858	76
Woolley.....	27,587	100	Knight.....	16,863	76
Mustard.....	17,359	98	Nolan.....	14,771	75
Edwards.....	29,358	98	Stewart.....	22,708	68
Washington.....	15,939	95	Lanciotti.....	13,053	67
Groos.....	22,290	91	Harris.....	16,875	66
Mickelson.....	22,247	91	Peper.....	22,992	65
Wolfe.....	18,725	90	Wessells.....	21,006	65
Houts.....	26,030	89	Group.....	240,614	74
Hammang.....	22,697	88	McCabe's group:		
Brekke.....	31,365	80	Mele.....	18,577	92
Group.....	274,432	93	Chalmers.....	21,725	87
Waddle's group:			Gray.....	33,357	84
Powell.....	46,024	103	Ayala.....	19,175	78
Pies.....	32,743	101	Kearney.....	15,056	75
Smith.....	29,955	96	Chazankin.....	12,536	75
Iverson.....	32,130	91	Callan.....	23,836	74
Hilliker.....	35,884	91	Nylund.....	17,330	70
Bentley.....	25,524	84	Hillman.....	10,807	63
Hart.....	19,119	86	Group.....	182,489	77
Cargile.....	21,486	83	Hatfield's group:		
Ginger.....	30,876	83	Furr.....	12,703	91
Yarborough.....	22,767	79	Pederson.....	16,695	83
Kohls.....	21,895	75	Allen.....	21,884	83
Group.....	334,788	91	Burgess.....	21,186	83
Benedict's group:			O'Brien.....	21,009	82
Brown.....	22,886	98	Baker.....	15,208	78
Lawing.....	27,175	98	Mansho.....	7,845	74
Strinz.....	18,607	95	Koberstein.....	22,885	74
Alfano.....	25,585	95	Taylor.....	9,276	73
Nordquist.....	13,579	93	Group.....	173,145	81
DuBois.....	25,031	89	Region.....	1,649,075	86
Solari.....	18,847	88			
Blake.....	24,775	87			
Filler.....	23,783	87			
Richardson.....	18,797	86			

## BULLETIN NO. 74, SEPTEMBER 5, 1967

To : All Western Region Sales Associates.

From : H. Glassner.

Subject : Profit Improvement Promotional Program, 'Indocin.'

"If it doesn't work in a week, forget it."

Now that's a clever slogan. It really should say, "If it does work in a week, you had better really forget it."

Here are some direct quotes from the current package circular for Butazolidin.

1. "Important Note. Butazolidin brand of phenylbutazone, cannot be considered a simple analgesic and should never be administered casually. Each patient should be carefully evaluated before treatment is started and should remain constantly under close supervision of the physician. . . ."

2. "Contraindications. Butazolidin, brand of phenylbutazone, is contraindicated in the presence of edema and in cases in which there is danger of cardiac decompensation. . . ."

Now, how many older patients . . . the patients with most of the aches and pains . . . the real crooks and cruds seen in everyday daily practice . . . just how many of these patients do not have some degree of cardiac decompensation or some degree of edema?

Yet, the term "contraindication" has medico-legal connotations. This part of the country has the highest rate of malpractice suits and, therefore, the highest rate of malpractice insurance. Why add fuel to the fire?

3. "Precautions. Patients receiving Butazolidin, brand of phenylbutazone, should remain under close supervision of the physician and should be warned to report immediately the recurrence of fever, sore throat, lesions in the mouth, or black or tarry stools. Specifically, it is recommended that periodic visits with the physician include :

- a. Verbal and physical examinations for indications of toxic reactions.
- b. Check of patient's weight to determine significant water retention.
- c. Complete blood counts at weekly intervals during the early phase of therapy and at intervals of two weeks thereafter to guard against the possibility of blood dyscrasias."

A complete blood count costs at least \$7 to \$10. That makes therapy much, much too expensive.

Let's take the kid gloves off and start slugging it out.

Let's stress the balance between efficacy and safety of 'Indocin'. Our literature doesn't say anything about complete blood counts under precautions or contraindications.

The annoying G.I. side effects of 'Indocin' can be easily minimized by simple dosage adjustment, taking the dosage with food, milk, or antacid.

Let's get back to selling 'Indocin'. Be certain that every physician understands that

Wherever there is pain, inflammation, and swelling in or around the joint with a resultant limitation of motion as there is in rheumatoid arthritis, ankylosing spondylitis, acute attacks of gout, or osteoarthritis of the hip—

Whether the condition is acute or chronic . . .

Therapy with 'Indocin' usually—

Relieves pain, reduces inflammation, and increases joint mobility on a simple dosage regimen that is relatively safe, often dramatically rapid in effect, and usually most economical.

'Indocin' is a great drug. Promote it like it was.

## BULLETIN NO. 77, SEPTEMBER 11, 1967

To : All Western Region Sales Associates.

From : H. Glassner.

Subject : Profit Improvement Promotional Program, 'Indocin.'

Let's dare to compare.

In the management of inflammatory lesions of the musculoskeletal system where there is pain, inflammation, and limitation of motion—as there is in rheumatoid arthritis, osteoarthritis of the hip, ankylosing spondylitis, and acute gout—what choice does the physician really have if he does not prescribe 'INDOCIN'?

Sure, he can use aspirin. But, the patient has probably already used aspirin before he visits his physician. Furthermore, no less an authority than Dr. Howard Polley at the Mayo Clinic has said

"... I wouldn't put 'Indocin' in the category of aspirin. I think it is more potent. But, if indomethacin is as good as aspirin, that is a pretty good claim in my view. That is a recommendation for indomethacin. . . ."

If he is a gambling sole—and almost no physician ever likes to gamble with his patient's welfare—he can prescribe Butazolidin. However, the current edition of the Goodman and Gilman, on pages 338-339, states the following about Butazolidin.

"... Phenylbutazone is poorly tolerated by many patients. Some type of side effect is noted in 10% to 45% of patients, and medication may have to be discontinued in 10% to 15%. Nausea, vomiting, epigastric discomfort and skin rashes are the most frequently reported untoward effects from phenylbutazone. . . ."

"... Its use should be restricted to short-term therapy of not more than one week during any one treatment period. Even then the incidence of disturbing side effects is about 10%. . . ."

He can prescribe steroids, the most potent anti-inflammatory compounds presently available. But there is general widespread agreement among qualified clinicians that steroids.

1. Should never be the initial agent used to treat rheumatoid arthritis.

2. Should be used only after a conscientious and unhurried trial of conservative measures fails to achieve satisfactory results.

3. Should not constitute the only measure of treatment.

If he wants just analgesic effect, Darvon will work just as well as aspirin, but Darvon has little or no anti-inflammatory activity. Its use is purely palliative. At best, treatment covers only one symptom.

Let's be rational. Do yourself and your physicians a favor. Before you do anything else, as soon as you get into the office, make sure that he realizes that

When there is pain, inflammation, and limitation of motion in or around a joint as there is in rheumatoid arthritis, ankylosing spondylitis, acute gout or osteoarthritis of the hip,

Whether the condition is acute or chronic,

For short-term or long-term use,

Therapy with 'Indocin' usually

Relieves Pain,

Reduces Swelling, and

Improves Joint Mobility

on a flexible dosage regimen that is usually effective, usually, safe, and always economical.

Remember, the product credit value of 'Indocin' is now 1.0. If your 'Indocin' sales are just average, you have automatically increased your income by \$22 per month.

Now, every extra bottle of 1000 'Indocin' that you sell is worth an extra \$2.80 in incentive payments.

Go get it.

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#### BULLETIN NO. 80, SEPTEMBER 13, 1967

To : All Sales Associates in the Western Region.

From : H. Glassner.

Subject : *Profit Improvement Promotional Program, 'Indocin.'*

If you are a timid sole, if you are a cautious 'Indocin' detailer, you can still find some Powerful Selling Sentences right in the F&DA approved package circular.

How about using these?

"In acute rheumatoid arthritis, or in acute flares of chronic rheumatoid arthritis, prompt improvement with relief of pain, tenderness, swelling, and stiffness will usually occur."

"In many patients with chronic rheumatoid arthritis, 'Indocin' produces a significant decrease in pain and stiffness within forty-eight hours. . . ."

"'Indocin' . . . has anti-inflammatory, analgesic, and antipyretic activity. It has a unique chemical structure which differentiates it from the salicylates, corticosteroids, phenylbutazone-like compounds, and cholechicine. Unlike corticosteroids, it has no effect on pituitary or adrenal function."

Use one, use two, or use 'em all. But be sure he understands that

Whenever there is pain, inflammation, and limitation of motion in and around a joint—as there is in rheumatoid arthritis, ankylosing spondylitis, osteoarthritis of the hip, and gout . . .

whether the condition is acute or chronic . . .

whether therapy is to be long-term or short-term . . .

therapy with 'Indocin'

relieves pain,

reduces inflammation,

and improves joint mobility

on a flexible dosage schedule that is usually effective, usually safe, and quite economical.

Remember, if your sales of 'Indocin' are just average, the new product credit value for 'Indocin' gives you an automatic \$22 per month increase in incentive payments plus the opportunity to earn \$2.80 extra for every bottle of 1000 'Indocin' you sell over your present average sales.

#### BULLETIN No. 85, SEPTEMBER 27, 1967

To: All Western Region Sales Associates.

From: H. Glassner.

Subject: *Profit Improvement Promotional Program, 'Indocin.'*

Don Epperson is brand new. He hasn't even been assigned to a territory yet. He is still waiting to go to West Point to complete his Basic Training. He doesn't know any better than to spend enough time putting a hard-hitting story on 'Indocin' together and then deliver it with conviction, enthusiasm, and force. He is temporarily working in a vacant territory.

Howard Perttula brought the following detail back, after working with Don just two days. Try it. It might put you in the top ten before Don gets assigned. By that time, he should be crowding our Top Ten Club. The selling time for this detail is less than three (3) minutes.

"Doctor, in the management of pain, inflammation, and limitation of motion associated with musculoskeletal diseases, there are many choices of therapy.

Basically, at one end of the continuum is Aspirin . . . at the other are steroids.

In between these two extremes, you can choose between phenylbutazone and 'Indocin'.

'Indocin' is chemically unique. It is not a steroid. It is not an aminopyrine derivative. Therefore it is distinctly different from phenylbutazone. Indeed, unlike phenylbutazone when 'Indocin' is used for prolonged therapy, the patient does not need to pay for periodic complete blood counts.

Most of the adverse reactions which occur with 'Indocin' are common with any anti-rheumatic drug. They usually are transient, easily controlled, and often disappear on continued treatment.

Yet, 'Indocin' is not a simple analgesic. 'Indocin' is a potent analgesic with pronounced anti-inflammatory properties which frequently affords prompt relief of acute rheumatoid arthritis and increased joint mobility within forty-eight (48) hours. In fact, the action of 'Indocin' is often so rapid that when it is used in an acute attack of gout, a marked reduction of pain often occurs within two to four hours.

Whenever the patient's problem involves pain, inflammation, redness, swelling, and limitation of motion in or around the joint . . . as in rheumatoid arthritis, osteoarthritis of the hip, ankylosing spondylitis, or gout—

whether the condition is chronic or acute.

whether therapy is to be short or prolonged.

'Indocin' usually provides a reduction in swelling, relief of pain.

Since most rheumatoid arthritic patients who present themselves to you with such problems are having an acute flare-up of their disease, you can maximize the benefits of 'Indocin' by starting the patient on one or two capsules of 'Indocin' three times a day . . . pushing the dose to a maximum of six capsules . . . until relief is obtained and then gradually tapering the patient off to the usual maintenance dose of two or three capsules a day.

Gastric irritation can be minimized by giving the dose of 'Indocin' after meals.

Doctor, will you use 'Indocin' in the management of these arthritic disorders either after Aspirin or before Steroids, so your patient can benefit from 'Indocin' that much sooner?"

Remember, every bottle of 1000 'Indocin' that you sell, over your normal average, is now worth an additional \$2.80 in incentive payments.

Pile it in!!!

Dr. McCLEERY. This Bulletin No. 83 advises the detail man to tell the physician:

Doctor, I'm certain that in your busy practice no day passes without several patients seeking your help from the misery inflicted by painful, reddened, swollen, feverish joints—the classic signs of inflammation.

The bulletin goes on to promote Indocin for "pain in the muscles." It urges the detail man to "convince" the physician that Indocin should be used "when the muscles around an inflamed joint are in spasm causing a limitation in motion" and for "just plain muscoskeletal [sic] aches and stiffness \* \* \*"

The unwarranted claims I have just mentioned appear repetitively in other bulletins of this same introductory time period. We regard these claims as outside the limits of indications in the approved labeling and therefore seriously misleading. In this connection, Bulletin No. 87, July 20, 1965, contains this statement of admission:

In fact, our guys are using a real expanded claim for "Indocin" on inflammation. They are consistently telling their doctors that \* \* \*

They repeat the quotes similar to the ones I mentioned just above.

Senator NELSON. So in the drug company's own bulletin this sentence is a confession that they are making claims over and above those approved by the FDA, is that not correct?

Dr. McCLEERY. Yes, it is correct that that is what these bulletins say.

Senator NELSON. Please go ahead.

Dr. McCLEERY. It appears quite clear that the detail men were being told to influence physicians to use Indocin for unapproved uses.

But the instruction to Merck detail men did not stop with the promotion of unapproved uses. The detail men were given slanted information to deemphasize side effects and other warnings.

Mr. Chairman, in the interest of saving the committee's time I will not recount all of the information in the Indocin package insert on contraindications, precautions, adverse reactions, and other warnings. In the composite, all of this information suggests that Indocin must be used cautiously, if at all, and with the expectation that serious side effects may occur.

Notwithstanding all of the warning advice in the package insert, the bulletins representing the period July 12 to August 4, 1965, instructed Merck detail men to convince physicians that "therapy with Indocin is safer." The implication was that Indocin is even safer than aspirin. The physician was told that the drug is contraindicated in pregnancy but nothing was said in the bulletins of instructions about its being contraindicated in children. The instructions stated that the only contraindications are pregnancy, ulcerative colitis, active peptic ulcer, and gastritis. This was false.

The instructions went on to say:

The other side effects are not serious. Some patients on therapy with Indocin may experience headache, dizziness or lightheadedness, and even some minor G. I. disturbances.

What the instructions did not disclose here were many serious side effects listed in the package insert. One such was that—

Indocin may cause single or multiple ulceration of the stomach, duodenum, or small intestine. There have been reports of severe bleeding and of perforation with a few fatalities.

Some other side effects listed in the package insert are drowsiness, tinnitus, mental confusion, depression and other psychic disturbances, blurred vision, stomatitis, pruritis, urticaria, angioneurotic edema, skin rashes, and edema.

In Bulletin No. 88, issued July 21, 1965, it was suggested that the detail men use this sales approach:

So, doctor, let's examine the relative lack of side effects of "Indocin."

In six out of ten patients on "Indocin," you need anticipate no adverse effects whatsoever.

In two out of three of these ten patients, some bothersome effects might occur. Bothersome is probably as severe an adjective as we can use to describe these effects because in most patients they are tolerable, and transient.

Mr. Chairman, as you know from our testimony last May there were a series of events that occurred between 1965 and 1967 which involved our dealing with Merck regarding its advertising and promotion of Indocin. The Assistant General Counsel, Food and Drugs Division, of the Department of Health, Education, and Welfare spoke publicly in October 1966 regarding our opinion as to the misleading nature of an Indocin advertisement which appeared in the Journal of the American Medical Association and elsewhere. Conferences were held with Mr. Henry W. Gadsden and his associates in the Merck management in November 1966.

Senator NELSON. So there is not any requirement on the part of the American Medical Association that the drug company make claims in their advertising in compliance with approved indications by the FDA?

Dr. McCLEERY. I don't believe that their code of approval of advertising copy includes the requirement that it conform to the package insert. They do have their own code, which they follow. And they state in each journal that it is applied to all advertising submitted to the journal before an ad is approved.

Senator NELSON. Do you mean to say that the American Medical Association, the AMA Journal, knowing the claim made in an ad in their medical journal goes beyond approved claims by the FDA is still willing to accept that ad?

Dr. McCLEERY. I would not want to say that the staff of the journal is aware of the information in the package inserts or that they are not, or why they make the judgments they do.

Senator NELSON. So far as you know, they do not require as a matter of advertising policy that the company inserting an ad comply with FDA-approved regulations as to that drug?

Dr. McCLEERY. So far as I know they do not, but I do not know just what their standards precisely might be.

Senator NELSON. Are you aware of the fact that any number of times ads have been put in the AMA Journal which made claims beyond approved indications by the FDA?

Dr. McCLEERY. I am aware, Mr. Chairman, that on quite a number of occasions we have felt the necessity to charge ads as false or mis-

leading in our view that have appeared in the Journal of the American Medical Association.

Senator NELSON. But I don't suppose I could expect you to comment on it, but it would seem to me that the great and distinguished medical profession ought to have the integrity to throw out any ad by any drug company that misleads the doctors. If there is anything a doctor ought to be able to rely upon, it is the official publication of the American Medical Association. I would assume that every doctor would say to himself that this is the distinguished leadership of the medical professions speaking to us, and what we say in their journal is honest, and I think it is an incredible disgrace that the AMA Journal wouldn't lay down a rule that any ad you put in here has got to comply with the FDA regulations. It shocks me, and I am ashamed of the leadership of this great profession respecting this kind of business misleading the doctors.

Please go ahead.

Dr. McCLEERY. Having given the Merck organization notice of our views of the status of their advertising and promotion of Indocin under the Federal Food, Drug, and Cosmetic Act, the firm did take action to correct its journal advertising.

Notwithstanding, we find in Merck instructional bulletins dated between April 5 and September 27, 1967, continued suggestions for open-ended uses and continued minimization of side effects. The bulletins, addressed to all associates western district, still bear the name of the same individual who apparently issued the bulletins back in 1965. There is nothing we see in the 1967 bulletins that suggest the firm had changed its basic philosophy and methods of promotion of Indocin from those employed in 1965.

Mr. Chairman, we have applied the principles of the advertising and labeling regulations in evaluating the Indocin bulletins apparently issued to Merck detail men in 1965 and 1967. Against these principles, we regard the bulletins as false or misleading in many details.

Other features of the bulletins which appear worthy of mention reflect disquieting attitudes of the firm's employees toward the medical profession and to the patient. Some of the statements in point in the bulletins are:

\* \* \* it is obvious that "Indocin" will work in that whole host of rheumatic crocks and cruds which every General Practitioner, Internist, and Orthopedic Surgeon sees everyday in his practice.

Tell 'em again, and again, and again.

Tell 'em until they are sold and stay sold!

For these entities ["rheumatic crocks and cruds"] he [the doctor] is presently prescribing steroids, aminopyrine-like butazones, aspirin, or limited analgesics like Darvon and the almost worthless muscle relaxants.

You've told this story now, probably 130 times. The physician, however, has heard it only once. So, go back and tell it again and again and again and again, until it is indelibly impressed in his mind and he starts—and continues—to prescribe "Indocin." Let's go.

Let's stand on our little old two feet this month and sell the benefits of "Indocin."

Take off the kid gloves. If he wants to use aspirin as base line therapy, let him use it. Chances are the patient is already taking aspirin. He has come to the physician because aspirin alone is not affording satisfactory, optimal effects.

Now, every extra bottle of 1000 "Indocin" that you sell is worth an extra \$2.80 in incentive payments. Go get it. Pile it in!!!

Mr. Chairman, if you have any questions I will be glad to answer them to the extent possible.

**Senator NELSON.** There was one other quote in Bulletin 74 referring again, referring this time to older patients and calling them "The real crocks and cruds." Now that quote is:

Now, how many older patients, the patients with most of the aches and pains, the real crocks and cruds seen in everyday and daily practice, just how many of these patients do not have some degree of cardiac decompensation and some degree of edema?

For a great and distinguished company to be referring to elderly citizens as "the real crocks and cruds" gives you some idea of the level of their attitude toward the patients. And apparently the attitude of the detail men and all the rest of them. The approved package labeling which I have here is dated effective May 1965; is that correct?

**Dr. McCLEERY.** Yes, sir.

**Senator NELSON.** Is a copy of the package labeling sent by the firm to all the detail men?

**Dr. McCLEERY.** Presumably so. It is required. We have no way of knowing for certain the intimate detail.

**Senator NELSON.** But the FDA does require that that be done?

**Dr. McCLEERY.** With every sample of drug that the detail man is given to give to doctors, there is required to be a package insert.

**Senator NELSON.** So, then, the 1965 instructional bulletins to detail men were issued after the package labeling had been in effect, is that not correct?

**Dr. McCLEERY.** Yes, sir.

**Senator NELSON.** Do you have a listing of all of the unapproved claims made by the company in the various bulletins examined?

**Dr. McCLEERY.** I don't have one before me. We have made one, and I have mentioned a number of them in my testimony. I think that that attitude is perhaps exemplified best in the early period of enthusiasm, which might be understandable if not condonable, in the period when a new drug comes on the market. However, it is less understandable in the year 1967, long after that introduction, and after our contacts on the principle of proper promotion of Indocin had led to agreement between the Commissioner and the top officer of Merck. I think the bulletins in 1967 are much more impressive in the way they express the value and indications of Indocin, and also what uses are suggested in this language, presumably by a regional sales manager, to develop copy for oral assertion by individual detail men to the doctor. This is much more subtle than the kind of language in the introductory period, but I think it is also quite instructive of the problem.

I would be glad to point out one or two instances of what I mean if you wish.

**Senator NELSON.** Please go ahead.

**Dr. McCLEERY.** You had made reference just a moment ago to a statement in Bulletin 74 dated September 5, 1967, on the "real crocks and cruds." In the same bulletin in which that statement is made, there is a reference on the second page which runs through, in a very subtle way, the whole pattern of promotion by this method in the time period of 1967. I will quote from it, Mr. Chairman. On page 2 it says—

**Senator NELSON.** Is that September 5, 1967, Bulletin 74?

**Dr. McCLEERY.** Yes, sir; on page 2. It says: "Wherever there is pain, inflammation and swelling in or around the joint with a resultant limitation of motion as there is in rheumatoid arthritis, rheumatoid

(ankylosing) spondylitis, acute attacks of gout, or osteoarthritis of the hips." On the surface, when this goes by quickly, it sounds like it is entirely within the indications described by the approved package labeling. But the fact of the matter is that it is an open-ended statement of indications, because it says "Wherever there is a pain, inflammation and swelling" use this drug, and the only limitation, and it is not a real limitation, is in bringing in the proper indications by the statements "as there is in rheumatoid arthritis." This is not a limiting statement. It only says wherever there is inflammation use Indocin, and there is inflammation in rheumatoid arthritis, and so forth. This runs through the whole time period of 1967.

Senator NELSON. And that statement I read to you previously about the older patients, that is:

Now, how many older patients, patients with most aches and pains, the real crocks and cruds seen in everyday practice, just how many of these patients do not have some degree of cardiac decompensation or degree of edema?

What is that in there for, cardiac decompensation and some edema?

Dr. McCLEERY. Well, there are competitive drugs which are mentioned throughout the bulletins of this time period. The characteristic of this time period is competitive selling, giving the detail men information which may or may not be proper about the dangers or effectiveness of competitive drugs. One of the competitive drugs does have warnings in its labeling about the possibility of causing edema. Therefore, they are saying that this would limit the value of the competitive drug in this particular class of patient. There is some truth in that.

Senator NELSON. Is it common that you may end up with muscular soreness and tenderness as a consequence of the edema?

Dr. McCLEERY. That would be difficult to answer, Mr. Chairman. As far as the patient is concerned, he might feel that he had aches in his muscles, because of the swelling, and very likely wouldn't himself localize it to muscle, but just to his lower extremity.

We said in our testimony that there was some slanting of information and I would like, if you wish, to describe what we meant by that statement.

Senator NELSON. Yes, if you would, please.

Dr. McCLEERY. I mentioned that the need to sell a product by one company in competition with somewhat similar products by other companies creates the need to draw limits of value between it and its competitors' products. This is going on a great deal during this time period.

One of the drugs which has to be discussed, in this competitive way, for the treatment of rheumatoid arthritis and other inflammatory diseases, is plain aspirin. The bulletin of July 7, 1967, Bulletin No. 66, on page 2, is an example of a description of the value of aspirin in comparison with Indocin. It says:

From those severely afflicted patients who are not adequately controlled by aspirin or Darvon, i.e., when pain killers are no longer giving adequate control—

I am sorry, it says—

when pain killers no longer give adequate control or when they only kill pain without reducing inflammation or improving joint mobility, Indocin should be tried promptly or even tried first.

It goes on to say on the same page:

Remember and make sure your physician realizes that, unlike aspirin and Darvon, Indocin has been found effective in not only relieving pain but reducing fever, swelling and tenderness, and increasing joint mobility in the symptomatic treatment of rheumatoid arthritis.

Now, it is very likely true that few doctors would be misled by this description of the effects of aspirin. I don't know how many might be, but in some real sense that is beside the point. The description here is an inaccurate description of the value of aspirin. It puts it in an unfair light in competition, because it puts aspirin together with Darvon, which is not an anti-inflammatory agent, and makes it appear that aspirin also is not an anti-inflammatory agent—that it is only good for the relief of pain. And when it no longer does that one simple thing, then you should turn to Indocin, or even maybe turn to Indocin first, because it implies, if it doesn't directly say, that aspirin only kills pain without reducing inflammation or improving joint mobility.

This is not true of the salicylates, of which aspirin is a member. It is not at all true that unlike aspirin, Indocin has been found effective in not only relieving pain but reducing fever, swelling, and tenderness. Aspirin and other salicylates will also, as has been shown in double-blind studies, reduce not only pain, but fever, swelling, and tenderness. They have reduced swelling in the joints. They have improved joint mobility in double-blind studies. This is a more subtle, much less blatant, approach than the 1965 bulletins, but nevertheless, in our view, slanted and misleading. There are many other examples.

Senator NELSON. You did say a few moments back that you had in going through the bulletins extracted from them all of the claims that were made beyond FDA-approved claims? Did I understand you to say that?

Dr. McCLEERY. Yes. We have really enumerated most of those, the most important and significant ones in our testimony as far as unapproved indications are concerned.

Senator NELSON. If there are any others that you didn't list in your testimony—

Dr. McCLEERY. Yes, I have another one in Bulletin 77, September 11, 1967, which is headed on page 1 by the statement: "Let's dare to compare."

Senator NELSON. Pardon?

Dr. McCLEERY. "Let's dare to compare," and I should mention that this, I feel, reflects a normal and even laudable urge on the part of companies to compete. That is not what we are faulting in this time period, but only describing that this characterizes the nature of the 1967 bulletins.

This one again happens to be on aspirin and salicylates, and it started off by saying, "In the management of inflammatory lesions of the musculoskeletal system, where there is pain, inflammation and limitation of motion," again parenthetically, "as there is in rheumatoid arthritis." It then repeats the proper list of indications. But it is always this combination of the very subtle enlargement created by mentioning inflammation, and whenever there is swelling, "as there is" in the list of indicated illnesses. This runs all the way through.

Then it turns to an authority that is well known in the field of arthritis and rheumatism, Dr. Howard Polley, of the Mayo Clinic.

But first it suggests, in the language of the bulletin here for the detail man:

Sure you can use aspirin, but the patient has probably already used aspirin before he visits his physician. Furthermore, no less an authority than Dr. Howard Polley of the Mayo Clinic has said, "I wouldn't put Indocin in the category of aspirin. I think it is more potent. But if Indocin is as good as aspirin, that is a pretty good claim in my view. That is a recommendation for indomethacin."

Now there is a break in the quote of Dr. Polley's opinion. The implication of this quote is, if it were indeed used by a detail man to a doctor, that Dr. Polley is saying that, since indomethacin is as good as aspirin, he would recommend Indocin instead of aspirin. I don't know if that is his view. Whether it is or not, it isn't the view of experts in the field in general. I haven't had a chance to locate this statement by Dr. Polley.

Senator NELSON. You say there is a break in the quote. You mean there was something more said by Dr.—what is his name?

Dr. McCLEERY. Polley. Yes, but I don't mean to imply anything more than to describe that there is a break in the quote. I am not suggesting that they have broken it at any particular point for any particular reason.

Senator NELSON. You don't know what the full quote is?

Dr. McCLEERY. No, sir. I don't know where it came from, where he said it or anything like that.

The bulletin goes on to say that—

If he [the physician] is a gambling soul—

And again I have to break the quote and make a parenthetical statement. I don't know whether this is a Freudian slip, but constantly the language used here spells soul "s-o-l-e." I assume he means "soul." The quote goes on to say—

If he is a gambling sole, and almost no physician ever likes to gamble with his patient's welfare. He can prescribe Butazolidin if he is a gambling sole.

Senator NELSON. He can prescribe what?

Dr. McCLEERY. Butazolidin, a competitive product.

Senator NELSON. That purports to be a quote from whom?

Dr. McCLEERY. I was quoting from this Bulletin No. 77, September 11, 1967.

Senator NELSON. What about contraindications? The July 12 instructional bulletin says,

Other than that (pregnancy) the only contraindications to therapy with Indocin are ulcerative colitis, active peptic ulcer, and gastritis.

Now, that isn't a correct statement, is it?

Dr. McCLEERY. Will you ask that again, please? I don't mean the whole question.

Senator NELSON. In the July 12 instructional bulletin they say,

Other than that (pregnancy) the only contraindications to therapy with Indocin are ulcerative colitis, active peptic ulcer, and gastritis.

Is that a correct statement?

Dr. McCLEERY. The statement that you are repeating from the bulletin is an incorrect statement in reference to the full range of contraindications as contained in the package labeling.

Senator NELSON. Since you have inserted the package labeling, that includes the full range of contraindications. Are there several more in addition to these here?

Dr. McCLEERY. No, sir; there aren't several more. We mentioned one by name in our testimony, and that was that the drug is contraindicated in children. That is not mentioned. There is another inflammatory disease of the intestinal tract which is contained in the package labeling as a contraindication and is somewhat similar to the ones that you were naming, called regional enteritis. That is not on this list. That is the other contraindication.

Senator NELSON. Of course the children—it covers a vast number of people in any event.

Dr. McCLEERY. Yes, I mentioned it was contraindicated in children.

Senator NELSON. Then the next sentence said,

These are not unusual signs as you know, Doctor, even aspirin causes some gastric complaints.

Isn't the intent of this sentence to play down the warning of the previous sentence?

Dr. McCLEERY. I would think so.

Senator NELSON. In Bulletin 84, July 14, 1965, it states:

Indocin equals or surpasses the effectiveness of Butazolidin.

Is that correct?

Dr. McCLEERY. If I may, I would like to avoid trying to give a definitive answer to that. The evidence of comparative studies of these two products are unknown to me. I do not know if they exist to an extent that would permit someone to make meaningful comparative claims against another product.

Senator NELSON. Continuing to quote from Bulletin 84, July 14, 1965, and this is the excerpt form the statement: "In therapeutic doses has a safety index comparable to aspirin." Is that correct?

Dr. McCLEERY. I would have to say that in my understanding of what I feel are the views of people that I have read who work in this field, aspirin, as varied within the dosages used, is really safer. But you are asking me a question, Senator, that I am not really an expert in.

Mr. GORDON. Do you know of any studies which indicate—perhaps you have already answered this—that Indocin equals or surpasses the effectiveness of Butazolidin? On what do they base that statement?

Dr. McCLEERY. I don't know what they base the statement on, but I must say I am not an expert in the field of these drugs. There are studies I have read, but I am not prepared to make a statement that would be—I am perhaps more reluctant to do it than the statements we are reading were reluctant to make the claims. I know of none that prove this.

Senator NELSON. On page 2 of the bulletin it is stated:

Lightheadness and dizziness occur occasionally with Indocin as with almost any other medication. For the most part these effects are very mild and very transient.

One of the leading physicians who evaluated Indocin for Merck, Dr. Rothernich, wrote to Merck on June 12, 1963:

The greatest deterrent to increase in dosage to effective level is the appearance of cerebral toxicity. This manifests itself clinically in excruciatingly severe headaches, dizziness, lightheadedness, disturbance of sensorium, a feeling that

the head is floating away or even separating from the body, and a feeling of detachment from reality.

Does this comment of evaluation by Dr. Rothermich compare with your own claim?

Dr. McCLEERY. The statements that you are reading are opinions of Dr. Rothermich that I haven't seen. They are similar to the kinds of experiences reported with Indocin, and which are included within the package labeling.

Senator NELSON. So they have played down in their instructional bulletin the effects that are described and required in the labeling, is that correct?

Dr. McCLEERY. Well, it seems that they have a diminution of the impact of the ideas which are being described.

Senator NELSON. On page 3 of the Bulletin No. 66 dated July 7, 1967, we find, you have mentioned this yourself previously:

Indocin should be tried promptly or tried first.

Now, in the AMA's 1967 edition of New Drugs, page 540, we find the following statement:

Present clinical experience indicates that this drug is as effective as the salicylates in patients with rheumatoid arthritis. However, its use is not necessary when salicylate therapy is effective. Although aspirin is still considered the drug of first choice, indomethacin may be tried if aspirin ceases to be beneficial or is no longer tolerated.

Is the statement by the AMA Journal representative of the viewpoint of the FDA?

Dr. McCLEERY. It squares with my own personal understanding of the view of men who are experts and have written on comparative drug trials. In the approved labeling of the drug Indocin, there are no such comparative claims of this sort. It is the kind of view that I was trying to express awhile ago. It is a most common view of the experts in the field that the salicylates are still the drug of first choice to use. They give much of the same benefits that Indocin does if not to all patients.

Senator NELSON. I want to thank you very much, Dr. McCleery. We appreciate your very fine statement and you and your staff associates coming here this morning to testify.

Does anybody have anything they wish to add to the statement?

We will resume hearings, then, again tomorrow morning at 9:30.

Thank you.

(Additional instructions from H. Glassner to All Western District Associates, undated, follow:)

To : All western district associates

From : H. Glassner

Subject : Indocin

The "Indocin" release meeting was great. However, several of you have asked for a concise Product Information Outline from which you can build your own presentation. Here are the "must know" facts on 'Indocin'. Put the words together so they sound like you. Remember, however, no presentation is a good presentation unless it creates prescription specification.

What is Indocin?

Indocin is an entirely new "anti-rheumatic" drug that affords ANTI-INFLAMMATORY ANALGESIC—AND ANTIPYRETIC ACTIVITY. The unique chemical structure of 'Indocin' differs entirely from salicylates, corticosteroids, colchicine and phenylbutazone.

*What is Indocin for?*

Indocin is effective in the management of both short-term and long-term—acute or chronic inflammatory lesions of the musculoskeletal system including:

- Degenerative joint disease of the hip (osteoarthritis);
- Gout;
- Rheumatoid spondylitis; and
- Rheumatoid arthritis.

*What will Indocin do?*

When inflammation is causing pain and limitation of motion, therapy with 'Indocin' will usually:

- Promptly relieve pain;
- Reduce fever, swelling, and tenderness; and
- Increase joint mobility.

*What are the advantages of Indocin?*

Indocin is rapid and effective in action. Relief of symptoms is prompt.

(a) In most patients with chronic rheumatoid arthritis, 'Indocin' usually relieves pain and stiffness within 48 hours.

(b) In acute rheumatoid arthritis, or arthritic flares of musculoskeletal pain—'Indocin' usually relieves pain, swelling, and tenderness, and fever within 48 hours.

(c) In acute attacks of gout, 'Indocin' is dramatic. Marked reduction of pain is common within two to four hours. Tenderness and heat subside within 24 to 36 hours, and swelling decreases in 3 to 5 days.

In degenerative joint disease—particularly osteoarthritis of the hip—'Indocin' takes a bit longer to work but has clinically provided RELIEF OF PAIN AND INCREASED RANGE OF MOTION.

*Indocin has an extended margin of safety*

Although 'Indocin' is second in potency only to the steroids—'Indocin' has a wide range of safety.

(a) Chemically, 'Indocin' is related to tryptophan, a naturally occurring amino acid. Unlike Butazolidin, it is not an aminopyrine derivative. Therefore, 'Indocin' does not have the well-documented poisonous effects of aminopyrine and related compounds.

(b) 'Indocin' has no effect on pituitary or adrenal function. Therefore, the well known and well documented side effects of steroids such as hirsutism, psychic disturbances, etc. are not problems in patients on therapy with 'Indocin'.

*Broad applicability*

Because 'Indocin' has an extended margin of safety, it can be safely used on any adult patient.

Because 'Indocin' works even in stubborn, long-standing, degenerative joint disease (osteoarthritis of the hip), it undoubtedly will be dramatically, excitingly effective in routine rheumatoid complaints.

*What is the dose of Indocin and how it is supplied*

(a) Indocin is available as a 25 mg. blue & white capsule.

The cardinal rule in dosage with Indocin is start low and go slow.

In chronic arthritides, the starting dose of 'Indocin' is 1 capsule b.i.d. or t.i.d. If response is inadequate, this dose may be increased by 1 capsule daily at weekly intervals. The new dose is continued until adequate response is obtained or until a maximum of 8 capsules per day is reached.

In acute arthritis, the starting dose of 'Indocin' is 1 capsule b.i.d. or t.i.d. If response is inadequate, one additional capsule per day may be added each day until an adequate response is obtained or until a maximum of 8 capsules daily is given.

In acute gout, the recommended dose of 'Indocin' is 2 capsules t.i.d. This dose may be increased to a maximum of 8 capsules per day if necessary.

In chronic gout, 1 capsule b. i. d. may be given with 'Benemid' to minimize the possibility of subsequent attack.

*What are the precautions of Indocin therapy?*

Unlike Butazolidin, reports of changes in the white blood count in patients on therapy with 'Indocin' have been extremely rare. In most reported cases, it has been impossible to implicate Indocin as the causative agent.

Therefore, unlike Butazolidin, we do not recommend weekly or bi-weekly blood counts in patients being treated with 'Indocin'. Periodic, simple hemoglobin determinations may be made by the physician on routine office visits.

In about six out of ten patients, no adverse reactions of any kind will occur. In about three out of ten patients, very mild transient and tolerable reactions will possibly occur. These reactions would include mild nausea, mild headache, mild dizziness, and the other minor nuisance effects. Usually, these effects will disappear with continued therapy even without dosage adjustment.

In only one out of ten patients were reactions severe enough to justify dosage reduction or discontinuance of therapy.

Learn these facts well enough to handle objections. Then, on every call make sure you leave the physician's office with him completely convinced that—

Whenever, the problem is oppressive joint pain associated with heat, redness, tenderness, and swelling;

When the muscles around an inflamed joint are in spasm causing limitation in motion;

Whether the tentative diagnosis is osteoarthritis of the hip, gout, rheumatoid arthritis, rheumatoid spondylitis, or just plain musculoskeletal aches and lumbago; or

For short-term use in acute conditions or long-term use in chronic conditions—

Indocin will afford prompt relief to three out of four patients—more effectively—with an extended margin of safety—at less cost—with fever tablets—less dosage adjustment—and, therefore fewer problems to the patient and to his physician than any other currently available agent.

Go get it. This is a big one.

H. GLASSNER.

To : All western district associates.

From : H. Glassner.

Subject : Indocin.

Here is the biggest potential volume product we have released since 'Decadron'. Automatic shipments are in the stores and in the jobbers.

Voluntary, repeat orders are pouring into the Branch. Advise your customers that 12 x 100 'Indocin' are packed in a compact, easy-to-handle shipping carton. This should become the basic unit of sale. Each time you ship a carton of 12 x 100 'Indocin' you put \$84.00 more on the bottom line. At 6%, that puts a little better than a brand new \$5.00 bill in your pocket.

If you haven't already done so—complete the fourth book of Programmed Instruction. Then, build a detail. Your Field Managers will be testing you on the information contained in Book No. 4.

No matter what else you say, repeat and repeat and repeat this theme until it is indelibly impressed in the physician's mind. Learn it cold. Believe it fervently. Communicate it effectively.

Whenever the problem is oppressive joint pain associated with heat, redness, tenderness, and swelling.

When the muscles around an inflamed joint are in spasm causing limitation of motion.

Whether the tentative diagnosis is osteoarthritis of the hip, gout, rheumatoid arthritis, rheumatoid spondylitis, or just plain musculoskeletal aches and stiffness.

For short-term use in acute conditions or long-term use in chronic diseases.

Indocin will afford prompt relief to three of four patients.

More effectively—with an extended margin of safety—at less cost—with fewer tablets—less dosage adjustment—and, therefore fewer problems for both the patient and the physician than any other currently available product.

Let's not make the mistake of trying to teach the physician to diagnose. 'Indocin' is for relief of pain due to inflammation. Let him decide when to use 'Indocin'. However, encourage him to use it early when it will do the patient the most good.

Get hot on this one. We're gonna lead them.

H. GLASSNER.

(The American Law Division opinion previously referred to follows:)

THE LIBRARY OF CONGRESS,  
LEGISLATIVE REFERENCE SERVICE,  
Washington, D.C., May 7, 1968.

To: Senate Subcommittee on Antitrust and Monopoly (attention Mr. Gordon).  
From: American Law Division.

Subject: Does Food and Drug Administration have authority over oral statements of drug manufacturer's representatives who contact physicians directly.

No specific authority is conferred on the Food and Drug Administration to deal with the matter in question. The Food and Drug Act deals, in pertinent part, with labels and labeling. A drug shall be deemed to be misbranded in several situations set forth in the law. See 21 U.S.C. § 352. We have located three court decisions involving prosecutions under the Food and Drug Act for oral representations which apparently were misstatements respecting the product to which they relate. None of these, however, were concerned with statements to physicians. In *U.S. v. Hohensee*, 243 F. 2d 367 (1957) the evidence was sufficient to sustain the conviction of the defendant who subsequent to shipment of harmlessly labeled food products in interstate commerce to pre-arranged towns, went to such towns to give lectures and distribute literature promoting the use of such products to promote health. The case of *Nature Food Centres, Inc. v. U.S.* 310 F 2d 67 held that defendants selling drugs identified on attached labels as dietary supplements could not meet branding requirements of Federal Food, Drug, and Cosmetic Act through sale of "lecture notes" concerning the drugs where some of the drugs were destined for sale at stores where notes were not available and, even at halls where lectures were delivered and drugs were available, notes were obtainable only upon payment of additional price In *U.S. v. Article of Drug, etc.* 362 F. 2d 923 the court held that the evidence supported the finding that the drug company claimant adopted as its own representation a radio broadcaster's claim that vitamins were efficacious for prevention and treatment of human disease, and that claimant intended its products to be used for general purposes recommended by broadcaster, as asserted by the government which charged misbranding in that claimant's catalogs failed to contain adequate directions for use.

These three cases involving oral statements would appear to have but limited application, if any, to the question presented. It seems to us that there is no clearly defined authority for the exercise of control by the Food and Drug Administration over oral statements of manufacturer's representatives to physicians in all situations.

HUGH P. PRICE,  
*Legislative Attorney.*

(Whereupon, at 10:35 a.m., the subcommittee recessed to reconvene at 9:30 a.m., Wednesday, September 18, 1968.)



## APPENDICES

### APPENDIX I

[From *Annals of the Rheumatic Diseases*, vol. 25, 1966, pp. 334-339]

#### INDOMETHACIN IN IN-PATIENT TREATMENT OF RHEUMATOID ARTHRITIS

(By D. A. Pitkeathly, N. R. Banerjee, R. Harris, and J. Sharp, Devonshire Royal Hospital, Buxton)

Indomethacin has been used in the treatment of rheumatic disease for over 3 years. Preliminary reports of the effectiveness of the drug were encouraging (Rothermich, 1963; Norcross, 1963) Katz, Pearson, and Kennedy (1963) also found the drug to be beneficial but treatment had to be discontinued in over 20 per cent of patients because of side-effects. Hart and Boardman (1963) showed that indomethacin produced a measurable reduction in swelling of the proximal interphalangeal joints in patients with rheumatoid arthritis and that, when a placebo and the drug were used alternately, significant rebound effects commonly occurred with the commencement of placebo treatment. Side-effects, principally headache, dizziness, dyspepsia, and mental disturbances, were frequent being observed in over 50 per cent. of patients treated with a dose exceeding 200 mg. A trial of the drug by Wanka, Jones, Wood, and Dixon (1964) showed that indomethacin was effective when compared with a placebo, and a comparative trial against phenylbutazone by Percy, Stephenson, and Thompson (1964) showed that 200 mg. indomethacin was approximately equivalent to 300 mg. phenylbutazone daily, although a decidedly higher incidence of side-effects occurred with indomethacin.

During this period of development of the drug it was supplied in tablet form and the doses used ranged from 150 to 400 mg. daily. Wanka and others (1964), using this preparation and range of dose, reported one case of intestinal haemorrhage and one of perforated gastric ulcer. Lövgren and Allander (1964) used a similar dosage in eighteen patients with rheumatoid arthritis, six of whom had a previous history of peptic ulcer but had negative barium meals immediately before treatment; five patients developed peptic ulcers, two of these having no previous history, and three of the five had severe bleeding.

During the past 2 years indomethacin has been supplied in capsule form and the manufacturers have recommended an initial dose of 50 mg. daily, gradually increasing to a maximum of 150 mg. The incidence of side-effects was stated to have fallen from 50 to 10-30 per cent of all treated patients (Today's Drugs, 1964) as a result of using capsules and more conservative dosage, and Clark (1964) reported satisfactory improvement in many patients of a large group with rheumatoid arthritis using this scale of dosage. Recently Hart and Boardman (1965) have compared 75 mg. indomethacin daily with 300 mg. phenylbutazone daily, in out-patients with rheumatoid arthritis. A double-blind crossover trial was carried out, each drug being given for a period of 28 days. No significant differences were found in the relief of symptoms although there was a greater reduction of morning stiffness with phenylbutazone. There were no significant differences in strength of grip or in improvement in ring sizes of proximal interphalangeal joints, but indomethacin tended to have a greater effect on the latter. The preference of patients was in favour of phenylbutazone. The incidence of side-effects of indomethacin in this short-term trial are not stated, but in long-term studies on patients with rheumatoid arthritis, osteo-arthritis, and ankylosing spondylitis, the authors found that 37 per cent of the patients developed side-effects of drug treatment.

The present study has been carried out to evaluate indomethacin in a dose of 50 to 100 mg. in the in-patient treatment of patients with rheumatoid arthritis. Salicylates are currently the mainstay of drug therapy while the patient is being

treated with rest in bed and splintage followed by graded exercises. It was our aim to decide if indomethacin could effectively replace salicylates under these circumstances.

Hajnal, Sharp, and Popert (1959) have drawn attention to the considerable effect of "spontaneous improvement" in hospitalized patients. In addition to rest in bed and splintage, other features such as increasing familiarity with hospital environment and in the case of strength of grip, practice in the use of the apparatus, contribute to the improvement shown. This must be dissociated from the effect of drug therapy before the value of a new drug can be assessed.

#### PATIENTS STUDIED AND METHODS EMPLOYED

34 women and eight men with classical and definite rheumatoid arthritis (1958 A.R.A. Criteria—Ropes, Bennett, Cobb, Jacox, and Jessar, 1959) were studied. Before entering the trial each patient spent one week settling into the hospital routine. During this period analgesia was provided by soluble aspirin and was maintained at the pre-admission dose provided that this did not exceed 4 g. daily. If the patient was already on corticosteroids, the dose was maintained at the pre-admission level during the first week and throughout the trial.

Patients were excluded from the study if they had known peptic ulceration or severe dyspepsia or were intolerant of aspirin, or if the grip test could not be adequately performed by reason of severe anatomical deformity of the hands or if the strength of grip exceeded 300 mm. Hg.

The patients were allotted alternately to indomethacin or soluble aspirin on entry. The first drug was given for a 2-week period and then the other drug was administered for a further 2 weeks, so that half the patients received indomethacin followed by soluble aspirin, and the other half received soluble aspirin followed by indomethacin. The soluble aspirin was specially coloured and flavoured and the patients were unaware of the identity of the tablets. It was given in a dose of 4 g. daily throughout the 2-week period. Indomethacin was given in a dose of 25 mg. twice daily for 2 days, followed by 25 mg. three times daily for 6 days and then 25 mg. four times daily for the remaining 6 days.

Of the 42 patients, 38 completed the study. Two patients were withdrawn while taking soluble aspirin, one because of severe deafness and the other on account of repeated vomiting. One patient developed profound dizziness on indomethacin and the drug had to be withdrawn. The fourth patient was given an incorrect dose of indomethacin during the second week of treatment and was therefore excluded from the analysis. Of the remainder, twenty patients had commenced the trial taking soluble aspirin and eighteen patients had started with indomethacin. Five of those starting on soluble aspirin were taking prednisolone with a mean daily dose of 9 mg.; seven of those starting on indomethacin were taking prednisolone with a mean daily dose of 10 mg.

*Clinical assessment.*—Assessments were carried out on the first day of the trial and thereafter at weekly intervals until the completion of the study. As far as possible the patients were assessed at the same time of day throughout and the daily physiotherapy was not given until the assessments had been made. Strength of grip of both hands were recorded weekly. Swelling of the proximal interphalangeal joints was measured using jeweler's rings. These rings were labelled from A to Z with intermediate half-sizes; the diameter of size A was 0.476 in. and the increase in diameter from size A to B was 0.015 in. The patients were questioned concerning headache, dizziness, and dyspepsia, and any other side-effects were noted. At the end of the study the patients' preference for one drug or the other was recorded.

## ANALYSIS OF RESULTS

The mean strength of grip at the commencement of the study and at weekly intervals throughout the trial was calculated for each series of patients (Table I).

TABLE I.—MEAN VALUES FOR WEEKLY ESTIMATIONS OF STRENGTH OF GRIP (MM. HG) FOR PATIENTS STARTING ON SOLUBLE ASPIRIN AND INDOMETHACIN

Starting drug	Soluble aspirin	Indomethacin
Number of cases	20	18
Grip (mm. Hg):		
Initial	145.65	159.28
Week 1	163.90	194.11
Week 2	173.60	194.50
Week 3	183.80	199.17
Week 4	188.30	202.06

<sup>1</sup> Aspirin.

<sup>2</sup> Indomethacin.

Improvement was most marked during the first week of treatment with both drugs and in this week the average improvement was almost twice as great in those starting on indomethacin as in those starting on soluble aspirin. In the second week the indomethacin group—although then on a slightly higher dosage, having changed from 25 mg. three times daily to 25 mg. four times daily—showed on average no improvement in mean strength of grip but the value in the soluble aspirin group continued to improve, so that after 2 weeks the difference had narrowed considerably. During the second half of the study both groups showed some further average improvement, which was again more steady in those starting on aspirin, who were now on indomethacin; over the whole of the second fortnight those now on soluble aspirin showed only half the improvement of the other group. The total improvement after 4 weeks was virtually identical in the two groups.

\* \* \* \* \*

TABLE IV.—SIDE EFFECTS ATTRIBUTABLE TO SOLUBLE ASPIRIN AND INDOMETHACIN IN 42 PATIENTS

Side effect	Drug	
	Soluble aspirin	Indomethacin
Headache	10	17
Dizziness	3	4
Deafness	6	0
Dyspepsia	19	10
Vomiting	3	1
Diarrhea	3	0
Rash	0	1
Sweating	1	1

\* \* \* \* \*

*Patient Preference.*—This is shown in Table V. All three patients who were withdrawn from the trial because of severe side-effects on one drug completed 2 weeks of treatment on the other drug and are shown as preferring that drug.

TABLE V.—*Patient Preference*

Preference:	Number of cases
For soluble aspirin	21
For indomethacin	13
None	7
Total	41

## DISCUSSION

The anti-inflammatory action of indomethacin has been demonstrated convincingly under experimental conditions. Winter, Risley, and Nuss (1963) showed that the drug had a powerful effect in inhibiting granuloma formation in rats. In addition, inflammatory oedema induced by carrageenin was suppressed. Boris and Stevenson (1965) found that indomethacin was the most powerful of a group of five anti-inflammatory agents in inhibiting the inflammatory reaction induced by carrageenin in rats, the others being flufenamic acid, mefenamic acid, oxyphenylbutazone, and phenylbutazone in order of decreasing potency. Under clinical conditions, Hart and Boardman (1963) confirmed this anti-inflammatory action using 150–300 mg. of the drug daily. In view of the high incidence of side-effects with this range of dose we wished to study the effect of indomethacin in a dose not exceeding 100 mg. daily in the in-patient treatment of rheumatoid arthritis and to compare it with soluble aspirin in a dose commonly used in these patients. Studies had already been carried out by Hart and Boardman (1965) and Thompson and Percy (1966) and the drug was found to have considerable therapeutic value in patients with a variety of rheumatic diseases.

In recent years salicylates have been shown convincingly to have anti-inflammatory properties in experimental animals. Spector and Willoughby (1963) showed that systemic sodium salicylate has an inhibitory effect on the volume of exudate in turpentine-induced pleurisy in the rat and causes a non-specific suppression of the action of many substances that increase vascular permeability. Kelemen (1963) studied acute inflammatory oedema in rats using 1<sup>1/2</sup> serum albumin. He considered that there were two components to the inflammatory response. One was inflammatory swelling which was diminished by salicylate. The other, a possible tissue component, preceded visible swelling, persisted after the oedema had disappeared, and was unaffected by salicylate. In view of this work on salicylates in experimentally-induced inflammation, it must be borne in mind that doses of 4 g. daily in patients with rheumatoid arthritis may have anti-inflammatory activity of the same order of magnitude as that shown by indomethacin in low dosage.

In this study we have used strength of grip and improvement in swelling of the proximal interphalangeal joints measured by jeweller's rings to assess the weekly improvement throughout the trial period. Analysis of mean strength of grip during periods of treatment with soluble aspirin and indomethacin has shown that drug effect was approximately one half of the effect attributable to spontaneous improvement. It has also been shown that indomethacin had a greater effect than aspirin in improving strength of grip and that this difference was just significant at the 5 per cent level. On the other hand, there was no difference between the two drugs in their effect in reducing swelling of the proximal interphalangeal joints and most of the improvement which occurred was the result of spontaneous improvement.

There was a greater preference of patients for soluble aspirin than for indomethacin in this trial. The incidence of headache during soluble aspirin treatment was surprisingly high, so that the patient preference can hardly be due to indomethacin headaches unless these were qualitatively different from the headaches reported during aspirin treatment. Greater pain relief from aspirin in the dosage used may have been important. Hart and Boardman (1963) stated that indomethacin had no analgesic action in the mouse or rat using methods then in use. The manufacturers claim, as a result of controlled clinical studies, that 50 mg. indomethacin is equal in analgesic effect to 600 mg. acetylsalicylic acid. If this is so, then the analgesia produced by aspirin in this study was much greater than that produced by indomethacin.

The high incidence of side-effects of indomethacin reported in the literature has made physicians cautious. Headache and dyspepsia were still fairly frequent in this study despite the low dosage employed and the slow build-up of the drug. On the other hand, the incidence of side-effects except headache differed little from that occurring with 4 g. soluble aspirin daily. There is little doubt that side-effects would have been reported less frequently with both drugs if patients had not been asked about specific symptoms. No serious complications such as gastro-intestinal hemorrhage occurred, but the trial was of short duration and patients with severe dyspepsia or known peptic ulcer were not admitted to it. It is to be noted that, in the studies of Hart and Boardman (1965) and Thompson and Percy (1966), cases of neurological disturbance and gastro-intestinal bleeding were reported and that these side-effects could be present after many months of treatment.

#### SUMMARY

A cross-over trial of indomethacin and soluble aspirin has been conducted in in-patients with rheumatoid arthritis. The indomethacin was increased from 50 to 100 mg. during the treatment period, but the dose of soluble aspirin was maintained at 4 g. daily.

A method of analysis has been used which dissociates drug effect from other factors which may lead to the improvement with time usually observed in hospitalized patients regardless of medication. This has re-emphasized the important contribution of these factors.

Comparison of the two drugs has shown that strength of grip improved to a greater extent during indomethacin treatment and that this result was just significant at the 5 per cent level. Decrease in swelling of proximal interphalangeal joints was very similar during treatment with the two drugs but 21 patients preferred soluble aspirin, whereas thirteen preferred indomethacin, and the remaining seven had no preference.

It is concluded that indomethacin should not replace aspirin in the routine treatment of in-patients with rheumatoid arthritis. However some patients appear to do better with indomethacin and it may therefore be useful in selected cases.

We wish to thank Professor J. H. Kellgren for advice and criticism in the preparation of this paper. Miss F. Bier performed the statistical analysis and we are greatly indebted to her.

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## APPENDIX II

[Reprinted from *Annals of Internal Medicine*, vol. 49, No. 1, July, 1958, printed in U.S.A.]

## RHEUMATOID SPONDYLITIS: MANIFESTATIONS AND MANAGEMENT\*

(By Aaron M. Lefkovits, M.D., F.A.C.P., and J. R. Thomas, M.D., Memphis, Tenn.)

Rheumatoid spondylitis is one of the most common arthritic diseases affecting young and middle aged men during their most productive years and, with the exception of trauma, is probably one of the most common causes of backache in this segment of the population. Its importance as a cause of morbidity and disability in young men is attested to by the numerous articles which appeared in the medical literature during the war years and thereafter. However, despite this keen interest, the disease in many patients is unrecognized during its early stages and is allowed to progress until irreversible deformities develop before the correct diagnosis is made and proper management for its control is instituted. It appears, therefore, that some aspects of this disease need further clarification, especially in regard to its earlier recognition and to the institution of proper and effective therapeutic measures.

## METHODS

The records of 267 patients in whom the diagnosis of rheumatoid spondylitis was made were carefully reviewed. Some of the available data pertinent to this study are indicated in table 1. With few exceptions, all patients were examined and treated by one of us (A. M. L.). Since this study was made at a Veterans Administration hospital, where the majority of patients are males, all these patients were of that sex. The diagnosis of rheumatoid spondylitis in every instance was made on the basis of the history, physical findings and radiographic evidence. Roentgenographic examination included A-P and lateral views of the lumbosacral, dorsal and cervical spines. Whenever indicated, special inclined views of the sacroiliac joints and oblique views of the lumbar and cervical spines were obtained. Blood studies included the following determinations: hemoglobin, white blood cell count, erythrocyte sedimentation rate and, in a few patients, C-reactive protein, total serum proteins, albumin, globulin and A/G ratio. The results are shown in table 2. Treatment consisted of physiotherapy, irradiation of painful areas of the spine, instruction in breathing and postural exercises, measures of rehabilitation, dietetic management, correction of static factors, braces, aspirin, and, in a few patients, hydrocortisone and Butazolidin. During the later period of this study only those patients were treated with irradiation of the spine who failed to respond to the other measures.

TABLE I.—CLINICAL FEATURES

	Number of patients	Percent
Family history of arthritis.....	25 of 201	12.4
Trauma.....	66 of 229	28.8
Subjective complaints of arthritis in peripheral joints.....	166 of 264	62.8
Objective signs of arthritis in peripheral joints.....	113 of 266	42.4
Radiographic changes in sacroiliac joints.....	267 of 267	100.0
Radiographic changes in hip joints.....	41 of 267	15.3
Calcification of ligaments.....	89 of 267	33.3
Osteoporosis.....	64 of 267	23.9

\*Received for publication June 4, 1957.

From the General Medicine and Rheumatology Section of the Medical Service, Veterans Administration Hospital, Kennedy Division, Memphis, Tennessee.

Requests for reprints should be addressed to Aaron M. Lefkovits, M.D., Chief, Section on General Medicine and Rheumatology, Veterans Administration Medical Teaching Group Hospital, Park Avenue and Getwell Street, Memphis 15, Tennessee.

TABLE 2.—LABORATORY DATA

	Hemoglobin			White Blood Cell Count			E.S.R. (Wintrobe Method)		
Gm. %	>14.5	>13.5	>10.0	<10.0	>10,000	>5,000	<5,000	>10 per hr.	<10 per hr.
No. of pts.	117	70	60	9	57	190	14	209	46
Percent	45.7	27	23.4	3.5	21.8	72.8	5.3	81.9	18
C-RP	Total Serum Protein		Albumin (Normal 3.0-4.5 gm. %)		Globulin (Normal 2.3-3.6 gm. %)		Reversal A/G Ratio		
Pos.	Neg.	Normal	Abnormal	Normal	Decreased	Normal	Elevated	A/G Ratio	
No. of pts.	23	3	35	0	32	2	25	9	7

## OBSERVATIONS

The age of onset (figure 1) of the disease varied from the second to the sixth decade; the youngest patient was 17 years and the oldest 54 years at the onset of the disease. The period of observation (figure 2) varied from a few months to as long as nine years. The greatest number, 153 (57.4%), were in their third decade at the time of onset of the disease (table 3). In 201 patients the presence or absence of arthritic disease in the family was recorded; of these, 25 (12.4%) gave a history of "arthritis" in some other member of the family. Trauma was given as a precipitating factor by 66 (28.8%) of 229 patients. Subjective complaints of peripheral joint involvement were present in 166 of 264 (62.8%); objective signs of peripheral joint involvement in 133 of 266 (42.4%); and sciatic radiation in 63 patients (23.5%). All patients had radiographic evidence of sacroiliac involvement. Calcification of the vertebral ligaments was present in 89 patients (33.3%), and osteoporosis in 64 patients (23.9%). Forty-one patients (15.3%) had hip joint involvement. These data are recorded in table 3, and graphs.

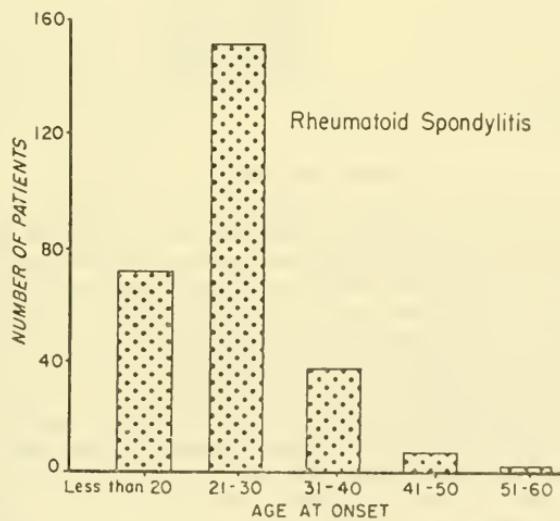


FIG. 1.

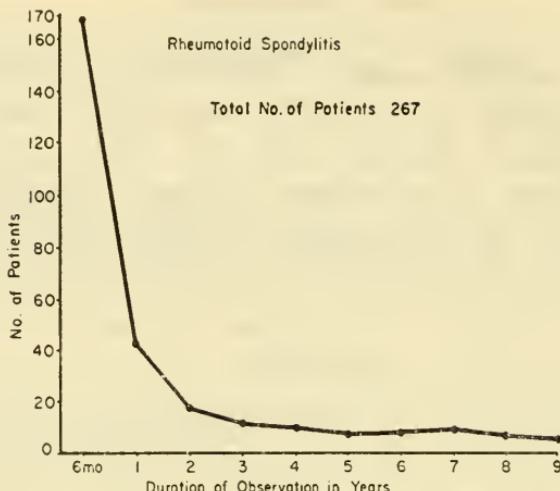


FIG. 2.

TABLE 3.—AGE AT ONSET AND DURATION OF OBSERVATION

Age at onset	Number of patients	Duration of observation	Number of patients
Less than 20.....	71	Less than 6 months.....	168
		More than 1 year.....	41
21 to 30.....	152	More than 2 years.....	17
		More than 3 years.....	11
31 to 40.....	37	More than 4 years.....	10
		More than 5 years.....	4
41 to 50.....	6	More than 6 years.....	5
		More than 7 years.....	6
51 to 60.....	1	More than 8 years.....	2
		More than 9 years.....	3
Total number of patients.....	267		

## MODE OF ONSET

The onset of the disease in the majority of the patients was insidious, generally over a period of several months or even years, and progression of the disease was interrupted by pain-free periods lasting several weeks or months. With each relapse, however, the symptoms were generally more severe and the duration of each episode was longer; ultimately the symptoms became more or less constant. Thus, there was a gradual increase in the severity of the patient's complaints. In a small number of patients the course of the disease was progressive and developed fairly rapidly, although they continued to have periods of exacerbations and remissions. The most common symptoms at the onset of the disease were stiffness and aching in the low back in the morning on awakening which would persist for half an hour or longer. With activity, the back would "limber up" and the aching and stiffness would gradually disappear toward the late forenoon, only to return toward the end of the day or during the night while the patient was lying in bed, awakening him. The severity of the backache varied considerably in different patients. Characteristically, it awakened the patient two or three hours after falling asleep. The patient would then get off the bed and walk about for one-half hour or longer to obtain relief; then he would return to bed, only to be awakened again in two or three hours, to repeat the process of walking to obtain relief. Patients whose disease was more severe repeated this process two to three times nightly, so that their rest and sleep were markedly disturbed and, as a result, their general well-being suffered. Their appetites became poor, and they lost weight. In some patients numbness of the lower extremities accompanied the aching and stiffness in the low back, and they "had to rub" their lower extremities to obtain relief.

In many patients the disease began as "catches, like pinching of a nerve" in one or the other hip region, at times radiating anteriorly to the iliac crests or abdomen. A few patients complained of weakness, or a sensation of "giving way" of the hip, alternating from one to the other hip. Radiation of pain to the buttocks, groins or along the posterior or, less often, the lateral aspect of the lower extremities to the knees or ankles occurred in some patients and, in a few, tingling in the toes on walking. In some, the backache was aggravated on coughing, sneezing, lifting weights or on any movement of the spine. The aching in the back at times was so severe that it seemed to "double up" the patient. A few subjects stated that the backache was accompanied by a tightness or "knot" in the abdomen, spasmodic contractions and rigidity of the abdominal musculature. Patients with involvement of the dorsal spine complained of soreness or migratory sharp pains in the chest during respiration and yawning, and had varying degrees of impaired chest expansion. The complaints were generally worse after periods of inactivity and, in some patients, during inclement weather. A few patients dated the onset of aching and stiffness in the low back to a time when they were treated in a hospital for some other apparently unrelated disease, such as gunshot wound, tonsillitis, etc. Three patients had been explored surgically for herniation of the nucleus pulposus at other institutions prior to our observation. A small number of patients had been believed to be psychoneurotic before the nature of their complaints was recognized, the correct diagnosis made and proper therapy instituted. In contrast, a few patients had only minor complaints referable to the spine, despite well developed deformities and advanced radiographic changes. These patients were generally older men in whom the disease was accidentally discovered while they were in the hospital for the treatment of an unrelated condition, such as hypertension, coronary artery disease, pulmonary emphysema, etc. Careful questioning of these patients revealed that in the past they had had only temporary discomfort in the back, consisting of aching and stiffness which did not interfere with the pursuit of their occupation or customary activities.

#### PHYSICAL FINDINGS

There was considerable variation in the objective findings. In the milder cases, during the early stages of the disease, no abnormal physical findings were noted and, as a rule, no abnormalities were seen on the radiograms. These were diagnosed on subsequent admissions to the hospital when definite objective abnormalities were found and radiographic evidence of the disease developed. In these instances we found the various leg and spinal maneuvers, particularly Lasègue's, Patrick's Gaenslen's and Ely's, and extent of chest expansion, of great help in arriving at the correct diagnosis.<sup>1</sup> Patients in whom the disease was more advanced presented some or all of the following manifestations in different degrees of severity: flattening of the lumbar spine, with partial or complete obliteration of the normal lumbar lordotic curve and exaggeration of dorsal kyphosis; flattening of the chest and impaired chest expansion; tenderness on pressure or percussion over the sacro-iliac joints and vertebral column; varying degrees of atrophy of the muscles of the spine; rigidity and impairment of some or all spinal movements; anterior fixation of the cervical spine; forward crouching deformity of the entire vertebral column, the so-called "poker spine"; and "en masse" movement of the entire spine. One patient had such marked anterior flexion and rigidity of the vertebral column that the longitudinal axis of the head was parallel to the floor. Several patients who had involvement of the hip joints had a characteristic waddling gait, walking with slightly flexed knees, forward-bent body and hyperextended neck, the upper extremities swinging in a plane posterior to that of the body as they shifted the pelvis from side to side with each step.

<sup>1</sup> Lasègue's Maneuver: Flexing the extended lower extremity upon the abdomen and noting the angle of flexion at which the pain in the low back is reproduced.

Patrick's Maneuver: With the patient in the supine position, the leg and thigh are flexed and the lower extremity is abducted and externally rotated at the hip.

Gaenslen's Maneuver: Hyperextension at the hip of the extended lower extremity while the opposite lower extremity is forcibly held by the patient in the knee-chest position.

Ely's Maneuver: With the patient in the prone position, the leg is flexed on the thigh and the lower extremity is hyperextended at the hip.

Chest Expansion: The circumference of the chest is measured at the level of the nipples at the end of full inspiration and expiration.

## LABORATORY DATA

Nine patients (3.5%) had less than 10 gm. % hemoglobin; 130 patients (52%) had mild to moderate decrease of hemoglobin concentration, and 117 patients (45%) had normal levels of hemoglobin. The white blood count was more than 10,000 per mm.<sup>3</sup> in 57 patients (21.8%); the highest count was 16,400; 14 patients (5.3%) had counts of less than 5,000 per mm.<sup>3</sup>; the lowest count was 3,200; 190 patients (72.8%) had normal white cell counts. The erythrocyte sedimentation rate was normal in 46 (18%) and abnormally elevated in 209 patients (81.9%); the highest level was 54 mm. in one hour. The C-reactive protein was determined in 26 patients; it was positive in 23 (88.4%) and negative in three patients. The total serum protein level was normal in all 35 patients in whom it was determined. The levels of the albumin and globulin fractions were determined in 34 patients. The level of albumin was normal in 32 and below normal in two patients; the globulin fraction was normal in 25 and abnormally elevated in nine patients; the highest level of globulin was 4.9 gm.%. The albumin-globulin ratio was reversed in seven patients (table 2).

## RADIOGRAPHIC CHANGES

It is generally known that the subjective manifestations of rheumatoid spondylitis may make their appearance long before definite evidences of the disease are seen in the radiograms of the sacro-iliac joints and/or of the spine. This interval may vary from a few months to a few years. A still greater difficulty is the recognition and correct interpretation of the early radiographic changes caused by the disease in the sacro-iliac joints, and particularly in the small diarthroidal joints of the vertebral column, namely, the apophyseal, the costovertebral and costotransverse articulations. The differentiation of these minor changes from the normally occurring variations in the size, shape and direction of the articular facets is extremely difficult. We have obtained considerable help from inclined views of the sacro-iliac joints taken with the x-ray tube tilted at an angle of approximately 35°, and oblique views of the lumbar and cervical spines. The inclined views of the sacro-iliac joints render clearer visualization of their margins and joint spaces, so that minor changes could be differentiated more readily from the normally occurring variations.

All patients had radiographic evidence of involvement of the sacro-iliac joints. These changes were varied: narrowing or widening of the joint spaces, irregular and indistinct joint margins, at times serrated edges, partial or complete obliteration of the joint spaces, spotty osteoporosis and irregular sclerosis of the adjacent sacrum and/or ilium. Similar abnormalities were noted in the apophyseal joints of the lumbar spine and the cervical spine. Adequate or correct recognition of such changes in the dorsal spine was rarely possible because of interference by overlapping rib shadows. Calcification of spinal ligaments was recognized in 89 patients (33.3%). The degree and extent of calcification also varied markedly; in some, it was present only in two or three isolated areas of the spine irregularly spaced; in others, it involved all the ligaments, produced the characteristic "bamboo effect," and transformed the entire spine into a rigid column. The hip joints were involved in 41 patients (15.3%); the abnormalities consisted of varying degrees of narrowing of the joint spaces, erosions of the cortices of the head of the femur and acetabulum, spotty osteoporosis, and irregular areas of sclerosis in the head of the femur and acetabulum.

In a few patients the margins of the symphysis pubis showed considerable irregularity and spotty osteoporosis of the adjacent bones. Irregularities of the lower margins of the ischia, spotty sclerosis and osteoporosis of the adjacent bones were also occasionally present. Osteoporosis of the entire spine was noted in 64 patients (23.9%).

TABLE 4.—RESPONSE TO THERAPY

	Number of patients	Response				Percent good or excellent
		None	Fair	Good	Excellent	
Physiotherapy.....	95	4	21	52	18	73.7
Radiation:						
1 course.....	116	13	17	57	29	174.1
2 courses.....	42	1	8	23	10	178.5
3 courses.....	7	0	1	3	3	185.7
Total.....	260	18	47	135	60	75.0

<sup>1</sup> Mean, 75.5 percent.

## ASSOCIATED AND INTERESTING MANIFESTATIONS

Three patients presented the triad of Reiter's syndrome, i.e., urethritis, iritis and arthritis involving both the spine and some of the peripheral joints. One patient had complete ankylosis of the temporomandibular joints and was unable to separate his jaws sufficiently to permit the intake of solid food. The condyles of the mandible were resected. Ankylosis recurred several months later; it was then relieved by arthroscopy and replacement of the condyles by Vitallium prostheses. Thirteen patients (4.5%) had iritis or iridocyclitis; six of these had involvement of the peripheral joints also. Five patients (1.8%) had psoriasis; all had involvement of the peripheral joints also. Thirty-six (13.5%) had various forms of anomalies of the spinal column; these are indicated in table 5.

## DIAGNOSIS

Rheumatoid spondylitis is easily recognized in patients in whom the disease is well developed. During its early stages, however, the diagnosis is often difficult. When objective manifestations of the disease, or corroborative radiographic changes, are lacking, the fatigability, weight loss and inconstant pain in joints or muscles of the spine are usually ascribed to psychogenic factors. Since there are no specific diagnostic tests, it is often impossible to arrive at the correct diagnosis until characteristic signs of the disease or abnormal radiographic changes appear. We found the following of considerable value in diagnosing the disease: (1) aching in any part of the back in a young man which occurred often during the night and induced him to get off the bed to "limber up"; (2) careful evaluation of results of leg and spinal maneuvers, and particularly the flexibility or rigidity of the spine on body movements; (3) meticulous examination of x-rays of the sacro-iliac joints, and especially of the inclined views of these joints. The laboratory data were of limited value in diagnosing the disease. The erythrocyte sedimentation rate and C-reactive protein were elevated in the majority of patients. The hemoglobin level was slightly to moderately decreased in approximately half of the patients.

TABLE 5.—*Associated and interesting manifestations*

Reiter's syndrome-----	3
Iritis -----	13
Psoriasis -----	5
Anomalies of vertebral column :	
Transitional lumbosacral joint-----	15
Spina bifida occulta-----	8
Spondylosis -----	6
Spondylolisthesis -----	3
Miscellaneous -----	4

## MANAGEMENT

Seven patients were asymptomatic at the time of observation and needed no therapy. The remaining 260 patients were treated with a variety of therapeutic measures. The complaints and findings of each patient were carefully considered prior to outlining his therapeutic regimen. Boards were placed under the mattress to prevent sagging of the bed, and the patient was advised to use no pillow under his head while lying in the supine position. Pillows were used until the head when the patient was lying on his side; they were also used until the lumbodorsal spine while lying in the supine position, or at some level under the trunk while lying in the prone position, provided such positioning of the pillow added to his comfort. Static factors such as tilting of the pelvis, inequalities in the length of the lower extremities or weak feet were corrected by construction of heel lifts, metatarsal bars, arch supports, etc. Dental care was given. Instruction in deep breathing and in exercise to correct postural abnormalities and to strengthen the muscles of the back and abdominal wall was given. Appropriate dietetic management was prescribed, i.e., patients who were underweight were given a high calorie and high protein diet (approximately 3,000 calories containing 100 to 150 gm. of protein daily), and overweight patients were placed on a reducing diet (800 to 1,200 calories). Dry or moist heat (infrared, diathermy, hydrocollator pack) was applied locally to the painful regions of the spine and to the involved peripheral joints. Ultrasonnd was applied in some instances. Occupational and corrective therapy was employed. When present, synovial fluid was aspirated in peripheral

joints, and hydrocortisone, 25 to 50 mg., was injected intra-articularly whenever this was deemed advisable. Aspirin, 0.3 to 1 gm. at four-hour or longer intervals, was used to control pain whenever needed. A few patients who complained of severe pains in the chest and abdomen of radicular distribution, or had spasm of the abdominal and intercostal muscles, were given hydrocortisone orally (50 to 100 mg. daily in divided doses), or phenylbutazone (400 to 600 mg. daily) for short periods of time. Radiation therapy<sup>2</sup> was administered with the Maximar 250 Kv or the Picker 200 Kv unit to painful areas of the spine through one to five portals in doses of 150 to 200 r as measured on the skin or air on alternate days for a total dose of 600 to 750 r to each area. The size of the portals over the sacro-iliac joints was 10 by 12 cm., and over the spine, 6 by 12 to 6 by 15 cm. The following factors were employed:

Filter—Thoreaus No. 2 or 0.5 mm. Cu and 1 mm. Al.

HVL—1 or 2 mm. of Cu.

If symptoms persisted, a second course of radiation therapy consisting of 450 to 600 r through each of two to five portals was given at an interval varying from six weeks to several months. A few patients were given a third series, several months later, consisting of 300 to 450 r through each of one to three portals. No serious toxic reactions were observed from irradiation. A number of patients complained of nausea and occasional vomiting, and a few had a moderate degree of leukopenia. The leukopenia was temporary. The nausea and vomiting were relieved by Dramamine in doses of 50 mg., or Bonamine in 25 mg. doses.

Most patients whose radiograms showed osteoporosis were placed on a so-called "osteoporotic regimen" for a period of three weeks. This regimen consisted of the following: (1) high calorie, high protein diet; (2) ascorbic acid, 100 mg. orally, daily; (3) depo-testosterone, 25 mg. intramuscularly, three times weekly; (4) stilbestrol, 1 mg. orally, daily; (5) vitamin B<sub>12</sub>, 100 µg intramuscularly, three times weekly. Sixty-three patients were fitted with braces (Taylor, three-point, Knight or von Wersowitz) to support the lumbodorsal spine. Plaster body casts with wedging or turn-buckles were employed in a few patients in an attempt to correct extreme forward-crouching deformities. Three patients had arthrodesis or arthroplasty of one or both hip joints. One patient had bilateral arthroplasty of the temporomandibular joints to relieve ankylosis of these joints, and one patient had arthrotomy and synovectomy of the left sternoclavicular articulation.

The nature of the disease in the light of presently held views was explained to the patient, with assurance of its generally benign character and eventual "burning out" of activity. The patient was encouraged to maintain an optimistic outlook. Emphasis was placed on the importance of maintaining good posture to prevent the development of deformities, of continuing muscle strengthening and breathing exercises, of the use of physiotherapeutic measures at home, and of the necessity of avoiding overexertion and upper respiratory tract or other infections. He was also advised to shift his position at sufficiently frequent intervals to prevent too great a "jellying" effect, to avoid bending over or lifting heavy objects, to bend his knees as in stooping, instead of bending his spine, when lifting objects off the floor, tying shoelaces, etc., and to avoid postures or activities that aggravated his discomforts. An attempt, not always successful, to rehabilitate the more severely affected patients was made by giving them vocational guidance and assistance in changing to an occupation which did not involve standing or sitting for prolonged periods, or arduous physical exertion.

#### RESULTS

It was difficult to evaluate the results of therapy correctly in terms of arrest of the disease, or the extent of relief of the subjective complaints. Duration of hospitalization could not be used as an indicator because many of our patients remained in the hospital for reasons other than their complaints referable to the spine. In estimating the effect of therapy, we relied generally on the degree of lessening of subjective complaints, especially decrease or disappearance of aching and stiffness, and extent of freedom of body movements. The degree of improvement was expressed as: (1) excellent: complete relief of subjective complaints and ability to resume regular occupation; (2) good: considerable relief of subjective complaints and ability to carry out body movements with relative freedom; (3) fair: some decrease of aching and stiffness; (4) no effect. The results are indicated in table 4.

<sup>2</sup> Radiotherapy was administered under the supervision of Dr. Ralph Braund, Dr. Walter Mendel and Dr. Benjamin Greenberg.

It is seen that "good" or "excellent" response was noted in 70 of 95 patients (73.7%) who were not given irradiation therapy, and in 125 of 165 patients (75.7%) who were given one to three courses of irradiation. There is therefore no significant difference between the two groups. We must emphasize, however, that the comparison is not valid because: (1) irradiation was only one of several therapeutic measures employed in the management of our patients, and (2) we did not evaluate separately the efficacy of physiotherapeutic measures apart from irradiation therapy. Our aim was to employ a therapeutic regimen which would expeditiously bring about a satisfactory remission of the disease and maintain this remission as long as possible.

#### DISCUSSION

During the course of this study we were impressed by the variability of the subjective manifestations and the general lack of correlation between subjective complaints, clinical manifestations, alleged disability and the roentgen manifestations, especially during the early stages of the disease. We became aware of the influence of the expected gain to be derived from the persistence of complaints in regard to awards of disability compensation in many of our veteran patients. Nevertheless, the diagnosis could be made with certainty in most of these patients. We found the following clinical features to be of value in diagnosing the disease during the early stages: (1) the complaint of aching and stiffness in any part of the lumbodorsal spine, occurring during the night, awakening the patient two to three hours after he had fallen asleep, and necessitating his getting off the bed and walking around in order to "limber up" and obtain relief; (2) the repetition of this process two to three times nightly; (3) the occurrence of stiffness and aching in any part of the lumbodorsal spine on awakening in the morning, but "limbering up" upon resumption of activity; (4) reaction of the patient to the performance of the various orthopedic maneuvers.

We were also impressed by the difficulty in correctly interpreting the earliest radiographic changes and their differentiation from the normally occurring variations in the margins of the sacro-iliac and apophyseal joints. We also became aware of the difficulties in estimating the extent of relief obtained separately from physiotherapy and from irradiation. This difficulty was partly due to the fact that the relief of subjective complaints occurred not infrequently two to four weeks after completion of irradiation therapy. In our experience, the best results were generally obtained from the combination of physiotherapy, irradiation, postural and muscle exercises, the judicious use of aspirin and correction of static factors and of established deformities by orthopedic procedures.

#### SUMMARY

The clinical features and roentgenographic signs in 267 patients with rheumatoid spondylitis are described. The difficulties in diagnosis encountered during the early stages of the disease are discussed, and methods found helpful by the authors in diagnosing the disease during its early stages are described. Management of the disease is discussed, and results of therapy in this series of cases are tabulated.

#### SUMMARIO IN INTERLINGUA

Es describite manifestationes clinic e le constataciones roentgenographic in 267 pacientes masculine con spondylitis rheumatoide. Le diagnose e le tractamento es discutite. Le etates del pacientes al tempore del declaracion del morbo variava inter le secunde e le sexte decennio. A judicar per le gravamines subjective del pacientes, affection de articulation peripheric esseva presente in 166 ex 264 casos (i.e. 62.8%). Signos objective de affection de articulation peripheric esseva presente in 113 ex 266 casos (i.e. 42.4%). In le majoritate del casos, le declaracion del morbo esseva insidioso. Le grados de severitate del dolor dorsal variava considerablemente in differente pacientes. In 63 casos (i.e. 23.5%) illo esseva accompaniate de radiation sciatic e de paresthesias. In le casos characteristic, le pacientes esseva eveliate perdolores dorsal duo a tres horas post addormir se. Alicunes habeva doloroso contracciones del musculos abdominal e acute dolores migratori in le thorace durante le respiration.

Le constataciones physic variava grandemente in differente pacientes. Observaciones frequente esseva aplatation del thorace e del spina lumbar, obliteratio del curva lordotic, exaggeration de cyphosis dorsal, dysfunction del expansion del thorace, rigiditate con movimento "como massa unite" del spina integre, e dys-

function del movimentos spinal. Le niveleo de hemoglobina esseva infra le norma in 55% del pacientes. Le numeration leucocytic esseva normal in 72,8%. Le sedimentation erythrocytic esseva anormalmente accelerate in 209 casos (i.e. 81,9%). Vistas oblique del articulationes sacro-iliac facilitava grandemente le recognition de precoce alterationes radiographic causate per le morbo. Le alterationes radiographic in le articulationes sacro-iliac e apophysee consisteva de restriction o allargation del spatio articular, de irregular o paucu distinete margines articular, e de obliteration partial o complete del articulationes. Evidentia radiographic de affection sacro-iliac esseva trovate in omne le casos. Calicification de ligamentos vertebral esseva presente in 89 casos (i.e. 33,3%), osteoporosis in 64 (i.e. 23,9%).

Tres pacientes exhibiva le triade del syndrome de Reiter. Un paciente habeva ankylosis complete de ambe articulationes temporamendibular. Dece-tres (i.e. 4,5%) habeva iritis o iridocyclitis. Cinque habeva psoriasis. E. 36 (i.e. 13,5%) habeva anormalitates del columna vertebral.

Le tractamento utilisava varie mesuras therapeutic. Factores static esseva corrigite. Le pacientes esseva instruite in como respirar e como executar exercitios postular. Un appropriate regime dietetic esseva prescrita. Calor humide o sielseesse applicate al region dolorose del columna vertebral e del afficite articulationes peripheric. Fluido synoviad esseva aspirate ab le articulationes peripheric. Hydrocortisona (25 a 50 mg) esseva injicite in le articulationes. Esseva utilitate therapia occupational e corrective. Aspirin (0,3 a 1 g) esseva administrata pro subjugar le dolores. Alicunes del pacientes recipeva diurnemente doses oral de hydrocortisona (50 a 100 mg) o de phenylbutazona (400 a 600 mg). Patients con osteoporosis recipeva regimes osteoporotic. Sexanta-tres esseva equipate con apparatus orthopedic. Cento sexanta e cinque recipeva inter un e tres cursos de roentgenotherapy profunde per inter un e cinque portales dirigite a areas dolorose del columna vertebral. Esseva administrata 600 a 750 r a omne portal in le prime curso, 450 a 600 in le secunde curso, e 300 a 450 r in le tertie curso. Cento vinti-cinque (i.e. 75,7%) obteneva bon o excellente responsas ab le irradiation. Le melior resultatas esseva effectuate per le combination de physiotherapy, irradiation, exercitios postural emuscular, uso judiciose de aspirina, e correction de factores static e de estableite deformitates per mesuras orthopedic.

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## APPENDIX III

SCHERING CORP.,  
November 8, 1967.

Hon. GAYLORD NELSON,  
U.S. Senate,  
Washington, D.C.

DEAR SENATOR NELSON: In the course of the July 24, 1967, hearings before the Subcommittee on Monopoly of the Senate Select Committee on Small Business, you referred to the "research . . . done by the National Institutes of Health with prednisone," and interrogated Mr. W. H. Conzen, President of Schering Corporation, concerning the report you had received from the NIH as to its expenditures in that regard.

You stated that you had been informed by NIH that they spent a total of \$2,114,000 in intramural research on prednisone and prednisolone in the years 1953 through 1967, and that, in addition, NIH had submitted to you a record of expenditures totaling \$14,384,144 in extramural research grant obligations for the period from 1953 through 1967.

You further stated (Transcript, p. 1032) : "This involved 639 grants from the period 1953 through 1967. These grants were not, I understand, exclusively to do research in prednisone and prednisolone, but in each of these 639 grants, research was done on prednisone and prednisolone, and that totaled \$14,384,144."

You asked that the listing of the intramural research expenditures and the table of the extramural research obligations be printed at the conclusion of Mr. Conzen's testimony. The interpretation given to these statements by the press throughout the country is typified by the following:

"Senator Nelson of Wisconsin pointed out that some 60 million dollars had been spent on prednisone research and development grants by the National Institutes of Health. So much for the claim that in this instance private industry carried the ball" (*Times Herald*, Carroll, Iowa).

"Nelson also took issue with Schering's claim of its contributions as the discoverer and developer of prednisone. He cited figures that the National Institutes of Health has spent some \$60 million in development and research grants on the drug" (The Washington Post, Washington, D.C.).

To clarify this matter, our Research Vice President requested NIH to furnish us information on this subject. We are now in receipt of its response, a copy of which we are enclosing. We ask that it, together with this communication, be incorporated into the record of the proceedings so that the latter may be more precise and complete.

Very truly yours,

IRVING II. JUROW,  
*Vice President and General Counsel.*

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,  
PUBLIC HEALTH SERVICE,  
NATIONAL INSTITUTES OF HEALTH,  
*Bethesda, Md., October 4, 1967.*

DEAR DR. GIBSON: This is in response to your recent inquiries concerning references made to NIH support of research on prednisone and prednisolone before the Senate Select Committee on Small Business Subcommittee on Monopoly, chaired by Senator Gaylord Nelson. We are enclosing a copy of the material supplied to the Committee in response to their request.

There are several points which need to be reemphasized, although they were fully explained by Senator Nelson during the hearing on July 24. As you will see in the attached document, the research reported (both intramural and extramural) covered prednisone and prednisolone for the fiscal years 1953 through 1967. The intramural funds reported were spent entirely on prednisone or prednisolone research. The footnote on the extramural research data (which was read into the hearing record by Senator Nelson, according to a member of his staff) reads as follows:

"Extramural obligations overestimate funds devoted to prednisone and prednisolone since all grants in which prednisone and/or prednisolone were named were counted in the total."

As far as the method of compiling the information is concerned, the Division of Research Grants, together with the Science Information Exchange, conducted a hand search of research projects either through the "Notice of Research Project" or through the Public Health Service Index for fiscal years 1953-1965.

A punch card run produced the data for FY 1966 and 1967. Projects included here are ones for which prednisone or prednisolone played a sufficiently prominent role to be included in the summary research protocol. We felt that we had no basis for attempting to prorate the amount of the grant award among its various elements. Therefore, we chose to explain the limitations of the data in the above-quoted footnote.

Your inquiries raise several other matters which are of some concern to us. The first is the matter of the misquoting of Senator Nelson in the *Washington Post* on July 25. We regret that our response to the Senate Committee has become embroiled in this controversy, but we are certain that you were not intending to involve or blame the NIH in any way for the error of the *Washington Post* or the fact that this error was picked up by other newspapers.

A second matter of concern to us was the statement in your letter of August 14:

"I particularly would question the purpose of the large sums expended in recent years after the activity of the drugs in question had been quite thoroughly explored by many laboratories throughout the world."

A review of our Research Grant Indexes indicates a shift of emphasis in recent years in projects involving these agents from subjects primarily within the purview of the National Institute of Arthritis and Metabolic Diseases or the National Institute of Allergy and Infectious Diseases to those more within the purview of the National Cancer Institute. This corresponds to our experience in our own intramural program as well, with the National Cancer Institute being the only Institute with increasing in-house research in recent years directly related to prednisone and prednisolone. We believe that this shift of emphasis may account for the level of expenditure which you questioned.

We welcome this opportunity to clarify our position with respect to this matter, and hope the attached information will meet your needs.

Sincerely yours,

JAMES A. SHANNON, M.D.  
Director.

ESTIMATED NIH RESEARCH EXPENDITURES FOR DIRECT OPERATIONS<sup>1,2</sup> RELATED TO PREDNISONE AND PREDNISOLONE, FISCAL YEARS 1953-56

Fiscal year	NCI	NIAMD	NINDB
1953.....	0	\$15,000	0
1954.....	0	50,000	\$18,000
1955.....	0	40,000	18,000
1956.....	\$10,000	30,000	10,000
1957.....	57,000	20,000	10,000
1958.....	13,000	10,000	0
1959.....	74,000	10,000	0
1960.....	19,000	0	0
1961.....	29,000	0	0
1962.....	11,000	0	0
1963.....	84,000	0	0
1964.....	231,000	0	0
1965.....	394,000	0	0
1966.....	409,000	0	0
1967.....	552,000	0	0
Total.....	1,883,000	175,000	56,000
Total NIH <sup>3</sup> .....			2,114,000

<sup>1</sup> Include contracts.

<sup>2</sup> Funds spent for purchase of drugs for the treatment of NIH Clinical Center patients not included.

<sup>3</sup> NIAID, none.

NIH EXTRAMURAL RESEARCH GRANT OBLIGATIONS, FISCAL YEARS 1953-67<sup>1</sup>

Fiscal year	Total funds	Number of grants
1953	\$156,237	12
1954	327,711	12
1955	394,817	18
1956	350,554	15
1957	326,554	21
1958	655,725	37
1959	783,502	44
1960	930,866	52
1961	1,134,729	56
1962	1,229,653	68
1963	1,338,872	60
1964	1,384,401	60
1965	1,683,464	69
1966	1,695,827	61
1967	1,991,232	254
Total	14,384,144	639

<sup>1</sup> Extramural obligations overestimate funds devoted to prednisone and prednisolone since all grants in which prednisone and/or prednisolone were named were counted in the total.

for fiscal year 1967.

<sup>2</sup> Incomplete data.

Note: Total intramural and extramural, \$16,498,144.



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